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# Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke (Review)

Allida S, Cox KL, Hsieh CF, Lang H, House A, Hackett ML

Allida S, Cox KL, Hsieh CF, Lang H, House A, Hackett ML.
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[Intervention Review]

# Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke

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## ABSTRACT

### Background

Depression is an important morbidity associated with stroke that impacts on recovery yet often undetected or inadequately treated. This is an update and expansion of a Cochrane Review first published in 2004 and updated in 2008.

### Objectives

*Primary objective*

• To determine whether pharmacological therapy, non-invasive brain stimulation, psychological therapy, or combinations of these interventions reduce the prevalence of diagnosable depression after stroke

*Secondary objectives*

• To determine whether pharmacological therapy, non-invasive brain stimulation, psychological therapy, or combinations of these interventions reduce levels of depressive symptoms, improve physical and neurological function and health-related quality of life, and reduce dependency after stroke

• To assess the safety of and adherence to such treatments

### Search methods

We searched the Specialised Registers of Cochrane Stroke and Cochrane Depression Anxiety and Neurosis (last searched August 2018), the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1), in the Cochrane Library, MEDLINE (1966 to August 2018), Embase (1980 to August 2018), the Cumulative Index to Nursing and Alllied Health Literature (CINAHL) (1982 to August 2018), PsycINFO (1967 to August 2018), and Web of Science (2002 to August 2018). We also searched reference lists, clinical trial registers (World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) to August 2018; ClinicalTrials.gov to August 2018), and conference proceedings, and we contacted study authors.


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**Selection criteria**

Randomised controlled trials comparing (1) pharmacological interventions with placebo; (2) one of various forms of non-invasive brain stimulation with sham stimulation or usual care; (3) one of various forms of psychological therapy with usual care and/or attention control; (4) pharmacological intervention and various forms of psychological therapy with pharmacological intervention and usual care and/or attention control; (5) non-invasive brain stimulation and pharmacological intervention with pharmacological intervention and sham stimulation or usual care; (6) pharmacological intervention and one of various forms of psychological therapy with placebo and psychological therapy; (7) pharmacological intervention and non-invasive brain stimulation with placebo plus non-invasive brain stimulation; (8) non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control; and (9) non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy, with the intention of treating depression after stroke.

**Data collection and analysis**

Two review authors independently selected studies, assessed risk of bias, and extracted data from all included studies. We calculated mean difference (MD) or standardised mean difference (SMD) for continuous data, and risk ratio (RR) for dichotomous data, with 95% confidence intervals (CIs). We assessed heterogeneity using the $I^2$ statistic and certainty of the evidence according to GRADE.

**Main results**

We included 49 trials (56 comparisons) with 3342 participants. Data were available for: (1) pharmacological interventions with placebo (with 20 pharmacological comparisons); (2) one of various forms of non-invasive brain stimulation with sham stimulation or usual care (with eight non-invasive brain stimulation comparisons); (3) one of various forms of psychological therapy with usual care and/or attention control (with 16 psychological therapy comparisons); (4) pharmacological intervention and various forms of psychological therapy with pharmacological intervention and usual care and/or attention control (with two comparisons); and (5) non-invasive brain stimulation and pharmacological intervention with pharmacological intervention and sham stimulation or usual care (with 10 comparisons). We found no trials for the following comparisons: (6) pharmacological intervention and various forms of psychological therapy interventions versus placebo and psychological therapy; (7) pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation; (8) non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control; and (9) non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

Treatment effects observed: very low-certainty evidence from eight trials suggests that pharmacological interventions decreased the number of people meeting study criteria for depression (RR 0.70, 95% CI 0.55 to 0.88; 1025 participants) at end of treatment, and very low-certainty evidence from six trials suggests that pharmacological interventions decreased the number of people with less than 50% reduction in depression scale scores at end of treatment (RR 0.47, 95% CI 0.32 to 0.69; 511 participants) compared to placebo. No trials of non-invasive brain stimulation reported on meeting study criteria for depression at end of treatment. Only one trial of non-invasive brain stimulation reported on the outcome <50% reduction in depression scale scores; thus, we were unable to perform a meta-analysis for this outcome. Very low-certainty evidence from six trials suggests that psychological therapy decreased the number of people meeting the study criteria for depression at end of treatment (RR 0.77, 95% CI 0.62 to 0.95; 521 participants) compared to usual care/attention control. No trials of combination therapies reported on the number of people meeting the study criteria for depression at end of treatment. Only one trial of combination (non-invasive brain stimulation and pharmacological intervention) therapy reported <50% reduction in depression scale scores at end of treatment. Thus, we were unable to perform a meta-analysis for this outcome.

Five trials reported adverse events related to the central nervous system (CNS) and noted significant harm in the pharmacological interventions group (RR 1.55, 95% CI 1.12 to 2.15; 488 participants; very low-certainty evidence). Four trials found significant gastrointestinal adverse events in the pharmacological interventions group (RR 1.62, 95% CI 1.19 to 2.19; 473 participants; very low-certainty evidence) compared to the placebo group. No significant deaths or adverse events were found in the psychological therapy group compared to the usual care/attention control group. Non-invasive brain stimulation interventions and combination therapies resulted in no deaths.

**Authors' conclusions**

Very low-certainty evidence suggests that pharmacological or psychological therapies can reduce the prevalence of depression. This very low-certainty evidence suggests that pharmacological therapy, psychological therapy, non-invasive brain stimulation, and combined interventions can reduce depressive symptoms. Pharmacological intervention was associated with adverse events related to the CNS and the gastrointestinal tract. More research is required before recommendations can be made about the routine use of such treatments.

## PLAIN LANGUAGE SUMMARY

### Pharmacological, psychological, and brain stimulation treatments for depression after stroke

**Review question**


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Do pharmacological treatments, non-invasive brain stimulation, psychological treatments, or combination treatments reduce the proportion of people with depression or the extent of depressive symptoms after stroke?

**Background**

Depression is common after stroke yet often is not detected or inadequately treated.

**Search date**

We identified studies by searches conducted on 13 August 2018.

**Study characteristics**

We included trials that reported on the use of pharmacological, non-invasive brain stimulation, psychological, and combination therapy interventions to treat depression after stroke. Mean age of participants ranged from 54 to 78 years. Studies were from Asia (30), Europe (11), North America (6), and Australia (2).

**Key results**

We included 49 trials (56 treatments) involving 3342 participants. Pharmacological treatments resulted in fewer people meeting the study criteria for depression and less than 50% reduction in depression scale scores at end of treatment. Psychological therapy reduced the number of people meeting the study criteria for depression at end of treatment. More people in the pharmacological treatment group reported central nervous system (in five trials) and gastrointestinal side effects (in four trials) than in the placebo groups. Information on side effects of other treatments was not provided.

**Certainty of the evidence**

Estimates of treatment effects were imprecise due to small numbers in most studies and recruitment of people with very different baseline characteristics. We rated the certainty of evidence as very low due to these and other limitations in study design.

**Conclusion**

Antidepressant drugs may benefit people with persistent depressive symptoms after stroke, but care is required in their use, as little is known about their side effects. Psychological therapy may offer a treatment option. Future research should include a broader group of people with stroke.


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**Summary of findings for the main comparison. Pharmacological intervention compared to placebo for treating depression after stroke**

**Pharmacological interventions compared to placebo for treating depression after stroke**

**Patient or population:** people with depression after stroke
**Setting:** inpatient, outpatient, or mixed
**Intervention:** pharmacological intervention
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with pharmacological interventions | | | | |
| Depression: meeting study criteria for depression at end of treatment (Analysis 1.1) | Study population<br>708 per 1000 | 499 per 1000 (348 to 642) | RR 0.70 (0.55 to 0.88) | 1025 (8 RCTs) | ⊕⊖⊖⊖ Very low[a,b,c] | |
| Depression: < 50% reduction in scale scores at end of treatment (Analysis 1.2) | Study population<br>821 per 1000 | 563 per 1000 (374 to 727) | RR 0.47 (0.32 to 0.69) | 511 (6 RCTs) | ⊕⊖⊖⊖ Very low[a,c,d] | |
| Depression: mean scores at end of treatment (Analysis 1.4) | | - | - | - | - | No totals |
| Neurological function: mean scores at end of treatment (Analysis 1.13) | | SMD 0.95 lower (1.44 lower to 0.45 lower) | - | 304 (4 RCTs) | ⊕⊖⊖⊖ Very low[a,b] | Lower score equals better neurological functioning |
| Adverse events: death - at end of treatment (Analysis 1.14) | Study population<br>19 per 1000 | 11 per 1000 (4 to 34) | RR 0.64 (0.20 to 2.07) | 848 (9 RCTs) | ⊕⊖⊖⊖ Very low[a,e] | |
| Adverse events: all - central nervous system events (e.g. confusion, sedation, tremor) (Analysis 1.15) | Study population<br>153 per 1000 | 262 per 1000 (177 to 370) | RR 1.55 (1.12 to 2.15) | 488 (5 RCTs) | ⊕⊖⊖⊖ Very low[a,e] | |


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| Adverse events: all - gastrointestinal effects (e.g. constipation, diarrhoea) (Analysis 1.15) | Study population | | RR 1.62 (1.19 to 2.19) | 473 (4 RCTs) | ⊕⊖⊖⊖ Very low[a,d] |
| | 193 per 1000 | 338 per 1000 (233 to 461) | | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio; SMD: standardised mean difference

**GRADE Working Group grades of evidence.**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of evidence as several studies were rated as high or unclear risk for multiple risk of bias domains.
[b]We downgraded the quality of evidence due to substantial heterogeneity (50% to 89%) observed.
[c]We downgraded the quality of evidence as the confidence intervals were wide.
[d]We downgraded the quality of evidence due to moderate heterogeneity (30% to 49%) observed.
[e]We downgraded the quality of evidence as the confidence intervals were very wide.

## Summary of findings 2. Non-invasive brain stimulation compared to sham non-invasive brain stimulation and/or usual care for treating depression after stroke

**Non-invasive brain stimulation compared to sham non-invasive brain stimulation and/or usual care for treating depression after stroke**

**Patient or population:** people with depression after stroke
**Setting:** inpatient, outpatient, or mixed
**Intervention:** non-invasive brain stimulation
**Comparison:** usual care and/or sham non-invasive brain stimulation

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with usual care and/or sham non-invasive brain stimulation | Risk with non-invasive brain stimulation | | | | |
| Depression: meeting study criteria for depression at end of treatment (Analysis 2.1) | - | - | - | - | - | No data available |




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| | | | | | |
|---|---|---|---|---|---|
| Depression: < 50% reduction in scale scores at end of treatment (Analysis 2.2) | - | - | - | - | No totals |
| Depression: mean scores at end of treatment (Analysis 2.3) | MD 6.63 lower (9.71 lower to 3.55 lower) | - | 495 (8 RCTs) | ⊕⊖⊖⊖ Very low[a,b,c] | |
| Depression: mean scores at end of follow-up (Analysis 2.4) | MD 2.60 lower (3.33 lower to 1.87 lower) | - | 170 (3 RCTs) | ⊕⊖⊖⊖ Very low[a,b] | |
| Neurological function: mean scores at end of treatment (Analysis 2.7) | SMD 2.21 lower (3.32 lower to 1.09 lower) | - | 290 (3 RCTs) | ⊕⊖⊖⊖ Very low[a,c,d] | |
| Adverse events: death - at end of treatment (Analysis 2.8) | - | - | - | - | No data available |
| Adverse events: all - central nervous system events (e.g. confusion, sedation, tremor) (Analysis 2.9) | - | - | - | - | No data available |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; SMD: standardised mean difference.

**GRADE Working Group grades of evidence.**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of evidence as several studies were rated as high or unclear risk in multiple risk of bias domains.
[b]We downgraded the quality of evidence as the confidence intervals were very wide.
[c]We downgraded the quality of evidence due to considerable heterogeneity (90% to 100%) observed.
[d]We downgraded the quality of evidence as the confidence intervals were wide.

## Summary of findings 3. Psychological therapy compared to usual care and/or attention control for treating depression after stroke

**Psychological therapy compared to usual care and/or attention control for treating depression after stroke**

**Patient or population:** people with depression after stroke
**Setting:** inpatient, outpatient, or mixed
**Intervention:** psychological therapy




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**Comparison:** usual care and/or attention control

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with usual care and/or attention control | Risk with psychological therapy | | | | |
| Depression: meeting study criteria for depression at end of treatment (Analysis 3.1) | Study population | | RR 0.77 (0.62 to 0.95) | 521 (6 RCTs) | ⊕⊖⊖⊖ Very low[a,b] | |
| | 750 per 1000 | 585 per 1000 (457 to 708) | | | | |
| Depression: < 50% reduction in scale scores at end of treatment (Analysis 3.2) | - | - | - | - | - | No data available |
| Depression: average change in scores between baseline and end of treatment (Analysis 3.3) | | MD 6.20 lower (8.24 lower to 4.16 lower) | - | 189 (3 RCTs) | ⊕⊖⊖⊖ Very low[a,c] | |
| Depression: mean scores at end of treatment (Analysis 3.4) | | - | - | - | - | No data available |
| Depression: meeting study criteria for depression at end of follow-up (Analysis 3.5) | Study population | | RR 0.85 (0.59 to 1.21) | 201 (3 RCTs) | ⊕⊖⊖⊖ Very low[a,c] | |
| | 603 per 1000 | 545 per 1000 (334 to 741) | | | | |
| Adverse events: death - at end of treatment (Analysis 3.17) | Study population | | RR 0.65 (0.26 to 1.66) | 831 (8 RCTs) | ⊕⊖⊖⊖ Very low[a,c] | |
| | 30 per 1000 | 22 per 1000 (10 to 50) | | | | |
| Adverse events: leaving the study early (including death) - all dropouts and withdrawals (Analysis 3.19) | Study population | | RR 0.83 (0.42 to 1.63) | 784 (8 RCTs) | ⊕⊖⊖⊖ Very low[a,c] | |
| | 52 per 1000 | 43 per 1000 (22 to 80) | | | | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence.**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.


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**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of evidence as several studies were rated as unclear or high risk in multiple risk of bias domains.
[b]We downgraded the quality of evidence as confidence intervals were wide.
[c]We downgraded the quality of evidence as confidence intervals were very wide.

### Summary of findings 4. Pharmacological intervention and a form of psychotherapy (combination) compared to pharmacological intervention and usual care or attention control (single) for treating depression after stroke

**Pharmacological intervention and a form of psychotherapy (combination) compared to pharmacological intervention and usual care or attention control (single) for treating depression after stroke**

**Patient or population:** people with depression after stroke
**Setting:** inpatient, outpatient, or mixed
**Intervention:** pharmacological intervention and a form of psychotherapy (combination)
**Comparison:** pharmacological intervention and usual care or attention control (single)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with pharmacological intervention (single) | Risk with pharmacological intervention and psychotherapy (combination) | | | | |
| Depression: meeting study criteria for depression at end of treatment (Analysis 4.1) | - | - | - | - | - | No data available |
| Depression: < 50% reduction in scale scores at end of treatment (Analysis 4.2) | - | - | - | - | - | No data available |
| Depression: mean scores at end of treatment (Analysis 4.3) | | MD 1.53 lower (2.10 lower to 0.96 lower) | - | 198 (2 RCTs) | ⊕⊖⊖⊖ Very low[a,b,c] | |
| Activities of daily living: mean scores at end of treatment (Analysis 4.5) | | MD 11.83 higher (0.27 higher to 23.40 higher) | - | 198 (2 RCTs) | ⊕⊖⊖⊖ Very low[a,c,d] | |
| Neurological function: mean scores at end of treatment (Analysis 4.6) | - | - | - | - | - | No totals |
| Adverse events: death - at end of treatment (Analysis 4.7) | - | - | - | - | - | No data available |


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| | | | | | |
|---|---|---|---|---|---|
| Adverse events: all - gastrointestinal effects (e.g. constipation, diarrhoea) (Analysis 4.8) | - | - | - | - | No totals |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial.

**GRADE Working Group grades of evidence.**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of evidence as both studies were rated as unclear risk in multiple risk of bias domains.
[b]We downgraded the quality of evidence as substantial heterogeneity (50% to 89%) was observed.
[c]We downgraded the quality of evidence as the confidence intervals were very wide.
[d]We downgraded the quality of evidence as considerable heterogeneity (90% to 100%) was observed.

**Summary of findings 5. Non-invasive brain stimulation and pharmacological intervention (combination) compared to pharmacological intervention and sham stimulation or usual care (single) for treating depression after stroke**

**Non-invasive brain stimulation and pharmacological intervention (combination) compared to pharmacological intervention and sham stimulation or usual care (single) for treating depression after stroke**

**Patient or population:** people with depression after stroke
**Setting:** inpatient, outpatient, or mixed
**Intervention:** non-invasive brain stimulation and pharmacological intervention (combination)
**Comparison:** pharmacological intervention and sham stimulation or usual care (single)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with pharmacological intervention (single) | Risk with non-invasive brain stimulation and pharmacological intervention and sham stimulation or usual care (combination) | | | | |
| Depression: meeting study criteria for depression at end of treatment (Analysis 5.1) | - | - | - | - | - | No data available |


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| | | | | | | |
|---|---|---|---|---|---|---|
| Depression: < 50% reduction in scale scores at end of treatment (Analysis 5.2) | | - | - | - | - | No data available |
| Depression: mean scores at end of treatment (Analysis 5.3) | | MD 4.09 lower (5.61 lower to 2.57 lower) | - | 665 (9 RCTs) | ⊕⊖⊖⊖ Very low[a,b,c] | |
| Activities of daily living: mean scores at end of treatment (Analysis 5.6) | | SMD 2.03 higher (1.21 higher to 2.85 higher) | - | 403 (5 RCTs) | ⊕⊖⊖⊖ Very low[a,b,d] | |
| Neurological function: mean scores at end of treatment (Analysis 5.8) | | MD 2.78 lower (4.13 lower to 1.44 lower) | - | 280 (4 RCTs) | ⊕⊖⊖⊖ Very low[a,b,c] | |
| Adverse events: death - at end of treatment (Analysis 5.9) | | - | - | - | - | No data available |
| Adverse events: leaving the study early (including death) (Analysis 5.11) | Study population | | RR 1.33 (0.32 to 5.58) | 300 (4 RCTs) | ⊕⊖⊖⊖ Very low[a,b] | |
| | 21 per 1000 | 29 per 1000 (6 to 125) | | | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio; SMD: standardised mean difference.

**GRADE Working Group grades of evidence.**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the quality of evidence as the confidence intervals were very wide.
[b]We downgraded the quality of evidence as several studies were rated as unclear or high risk in multiple risk of bias domains.
[c]We downgraded the quality of evidence as substantial heterogeneity (50% to 89%) was observed.
[d]We downgraded the quality of evidence as considerable heterogeneity (90% to 100%) was observed.


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# BACKGROUND

## Description of the condition

Depression and anxiety disorders are important sequelae of stroke. These mood disorders occur in up to half of people during the first year after onset of stroke, although estimates differ between studies due to varying definitions, populations, exclusion criteria, and timing of assessments (Ayerbe 2013; Hackett 2014). Inconsistent research findings are also due to the complexity of recognition, assessment, and diagnosis of an underlying mood disorder associated with acute stroke and cognitive, language, and other impairments. In addition, people with stroke may experience a variety of behavioural syndromes that are more specific to brain injury, including indifference, emotional lability, disinhibition, unawareness of illness (anosognosia), and difficulties with verbal 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 diagnosis of major depression and other depressive illnesses may mis-attribute features of ischaemic brain injury to depression (House 1987; Johnson 1991). Although several depression screening tools have been validated (against a structured clinical interview) for use in people with stroke (Turner 2012), in practice, researchers use a range of methods to diagnose depression - a psychiatric interview to apply standard diagnostic criteria such as those provided in the *Diagnostic and Statistical Manual of Mental Disorders* (e.g. DSM-IIIR, DSM-IV, DSM V) (APA 1987; APA 1994; APA 2013), or psychiatric rating scales such as the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), or a rating scale of mood based on self-assessment.

Although controversy continues about whether depression after stroke is predominantly caused by physical factors (such as stroke lesion location) (Carson 2000), or by a person's psychological response to stroke, evidence suggests that clinically diagnosed stroke-associated depression is similar in frequency and nature to depression among older people with other chronic illnesses (Burvill 1996; Burvill 1997; Sharpe 1990). Although 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 systematic reviews of high-quality observational studies (Hackett 2014). Although some people recover spontaneously, apparently undergoing a grief-like depressive adjustment reaction, up to one-third of people have depression that persists during the first year or longer after stroke onset (Astrom 1996; Herrmann 1998). Those 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 comorbid conditions. However, evidence provided by Parikh 1990 and Sinyor 1986 suggests that abnormal mood may impede rehabilitation by impairing physical function (Ayerbe 2013), as well as cognitive function (Robinson 1986), and by contributing to stress on carers (Anderson 1995a). Furthermore, stroke-associated depression may be associated with 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 comorbid conditions (Katona 1995).

## Description of the intervention

We considered three broad interventions.

- Pharmacological interventions designed to treat depression: several classes of relevant pharmacological agents include selective serotonin reuptake inhibitors (SSRIs) (e.g. fluvoxamine, fluoxetine, sertraline, citalopram, paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine, milnacipran, sibutramine), monoamine oxidase inhibitors (MAOIs) (e.g. moclobemide), tricyclic antidepressants (TCAs) (e.g. nortriptyline, imipramine, clomipramine), and other antidepressant medications including psychostimulants (e.g. methylphenidate), mood stabilisers (e.g. lithium), or benzodiazepines.
- Non-invasive brain stimulation: electroconvulsive therapy (ECT) involves the brief passage of an electrical current through the brain via electrodes applied to the scalp to induce a generalised seizure (i.e. a fit or convulsion). The seizure comprises two components: a central element - the ictus involving depolarisation (i.e. discharge of neurotransmitter chemicals) of brain cells - and a peripheral element consisting of convulsive, jerking movements of the body, although this is now modified due to use of a short-acting anaesthetic and muscle relaxant, as part of what is called modified ECT. Modified ECT replaced the crude equipment and techniques of unmodified ECT used in the mid-1950s. The seizure is detected by electrodes placed on the scalp to monitor brain electrical activity (i.e. EEG). The ECT electrodes can be placed on both sides of the head (bilateral placement), or on one side - usually the right side of the head (unilateral placement). Passage of an electrical current through the skull to the brain is necessary to trigger a seizure. In this update, we broadened the review to include other non-invasive brain stimulation techniques such as (1) transcranial magnetic stimulation or repetitive transcranial magnetic stimulation (TMS or rTMS, where a magnetic 'coil' is placed near the head of the person receiving the treatment without making physical contact); (2) transcranial direct current stimulation (tDCS, where a constant, low current is delivered directly to the brain area of interest via small electrodes); (3) cranial electrotherapy stimulation (CES, where a small, pulsed electrical current is applied across a patient's head); and (4) magnetic seizure therapy (MST), a type of convulsive therapy that involves replacing the electrical stimulation used in ECT with a rapidly alternating strong magnetic stimulation.
- One of various forms of psychological therapy (talking therapy) designed to treat depression: as many therapies are available, 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 people develop their social problem-solving skills and adjust to the emotional impact of stroke. All interventions had to have a psychological component - talking, listening, support, advice; they had to be based on a theory of talking therapy; had to be structured and time-tabled as a talking therapy; and had to be delivered by somebody with some explicitly stated training in and supervision of therapies. The person-professional interaction could take place in person,


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via telephone, or through other media. We did not include web-based interventions even if mediated by a healthcare professional. We did not include interventions based upon self-management or supported self-management.

We further considered these combinations of three broad interventions.

- Pharmacological intervention and one of various forms of psychological therapy versus pharmacological intervention plus usual care and/or attention control.
- Non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention plus sham stimulation or usual care.
- Pharmacological intervention and one of various forms of psychological therapy versus placebo plus psychological therapy.
- Pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation.
- Non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control.
- Non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

### How the intervention might work

Pharmacological interventions are thought to alter the synaptic transmission process within the brain to increase neurotransmission, for example, SSRIs are intended to block the resorption of serotonin, SNRIs are designed to increase the levels of serotonin and norepinephrine, and TCAs are designed to block the reuptake of norepinephrine.

During modified ECT, a small amount of electrical current is passed briefly across the brain to cause an artificial epileptic fit that affects the entire brain. Repeated ECT is believed to alter chemical pathways in the brain that are responsible for depression. The exact mechanism of action of rTMS, tDCS, and CES remains unclear. They are thought to induce intracerebral current flow and increase or decrease neuronal excitability and/or activate nerve cells in the specific area being stimulated. rTMS involves replacing the electrical stimulation used in ECT with a magnetic stimulus, which is purported to produce similar clinical effects but without the cognitive side effects.

Psychological therapy focuses on changing thinking, emotional, behavioural, and relationship patterns. During psychological therapies, trained therapists work with individuals to help them see patterns in their thoughts, emotions, behaviours, or relationships that may be problematic. The therapist's role is to help a person understand these patterns while assist that person in developing ways to overcome them.

### Why it is important to do this review

Although depression may influence recovery and outcomes following stroke, many (perhaps most) people with stroke do not receive effective treatment because their mood disorder is undiagnosed or is inadequately treated. The UK National Sentinel Audit found that 25% of patients were not screened for depression, and only 60% of those identified as needing support received it. Ebrahim 1987a found that few people with stroke-associated depression had been given antidepressants following discharge from hospital, and House 1989 reported that general practitioners and hospital doctors had a passive attitude toward therapy. On the other hand, some more recent studies have found antidepressant prescribing persisting long term but with little attempt to match prescribing to need (Paul 2006). Although this variability may reflect 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. For example, it is not clear that in other settings, antidepressants are of benefit for mild or moderate depression of the sort that is common after stroke (Fournier 2010).

Indirect evidence of the effectiveness of pharmacological and psychological treatments for depression (and anxiety) for older people in general, and for those with associated physical illness, is available in several published reviews (Gill 2000; Kirsch 2008; Lima 2001; McCusker 1998; Mittmann 1997; Wilkinson 1997). However, because of the possibility that depression after stroke may differ in important ways, it may be inappropriate to extrapolate these data to people with stroke. Use of rTMS, tDCS, and CES in people with stroke is relatively new, and few data are available to guide clinical decision-making.

We undertook and updated a systematic review of all randomised controlled trials (RCTs) (published and unpublished) of pharmacological agents, non-invasive brain stimulation, psychological therapies, or their combination for treatment of depression after stroke. This is an update of a Cochrane Review first published in 2004 and last updated in 2008.

## OBJECTIVES

### Primary objective

- To determine whether pharmacological therapy, non-invasive brain stimulation, psychological therapy, or combinations of these interventions reduce the prevalence of diagnosable depression after stroke

### Secondary objectives

- To determine whether pharmacological therapy, non-invasive brain stimulation, psychological therapy, or combinations of these interventions reduce levels of depressive symptoms, improve physical and neurological function and health-related quality of life, and reduce dependency after stroke
- To assess 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 randomised controlled trials (RCTs) only. 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 inclusion criteria, but from which no outcome data were available (neither from the report of the trial nor from the study authors), could not contribute meaningfully to a pooled estimate of effect. These trials were regarded as 'dropouts' rather than as ineligible.


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### Types of participants

We defined stroke according to clinical criteria, including cerebral infarction, intracerebral haemorrhage, and 'uncertain' pathological subtypes. We excluded trials of people 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 people with SAH. There were no restrictions on the basis of age, sex, or other characteristics. 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 2008a).

The diagnostic categories of depression considered were:

- depressive disorder, as defined by symptom scores on a standard screening instrument - scoring above a pre-defined scoring threshold;
- major depression, as defined by the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IIIR, DSM-IV, DSM-V; APA 1987; APA 1994; APA 2013), or similar diagnostic criteria; and
- dysthymia or minor depression, as defined by DSM or other standard diagnostic criteria.

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

### Types of interventions

We included the following interventions.

- Comparison between a pharmacological intervention and placebo for treatment of depression after stroke. Specific pharmacological agents included tricyclic antidepressants (e.g. nortriptyline, imipramine, clomipramine), selective serotonin reuptake inhibitors (SSRIs) (e.g. fluvoxamine, fluoxetine, sertraline, citalopram, paroxetine), monoamine oxidase inhibitors (MAOIs) (e.g. moclobemide), and other antidepressant medications. Trials of mood stabilisers (e.g. lithium) or of benzodiazepines and psychostimulants (e.g. methylphenidate) were analysed separately.
- Comparison between non-invasive brain stimulation and sham stimulation or usual care for treatment of depression associated with stroke.
- Comparison between psychological therapy and usual care and/or attention control for treatment of depression after stroke. We included any psychological therapy that involved direct person-professional interaction. The content of the interaction could vary from counselling to specific psychological therapy, provided it was directed at helping people develop their social problem-solving skills and adjust to the emotional impact of stroke. All interventions had to have a psychological component - talking, listening, support, advice - and had to be based on a theory of talking therapy; had to be structured and time-tabled as a talking therapy; and had to be delivered by somebody with some explicitly stated training in and supervision of therapies.

Alternatively, we included their combinations.

- Pharmacological intervention and one of various forms of psychological therapy versus pharmacological intervention plus usual care and/or attention control.
- Non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention plus sham stimulation or usual care.
- Pharmacological intervention and one of various forms of psychological therapy versus placebo plus psychological therapy.
- Pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation.
- Non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control.
- Non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

Exclusions included the following.

- Interventions with an agent or therapy that was being evaluated primarily for other reasons (e.g. to improve physical function, to provide neuroprotection, to facilitate neuroregeneration), even if the intervention was a recognised treatment for depression, and even if a standardised depression scale was administered at baseline and at outcome assessment (these trials are included in a separate systematic review, with depression as a secondary endpoint (Mead 2012)).
- Interventions provided with the sole purpose of educating or providing information.
- Occupational therapy (including leisure therapy and other rehabilitation services).
- Acupuncture or electro-acupuncture.
- Herbal medicines.
- Interventions that involved visits from stroke support workers, unless there was a clearly defined psychological component. Attention control in psychological therapy trials can include non-specific interventions such as relaxation classes or follow-up with a clinician who has no psychological training.

### Types of outcome measures

#### *Primary outcomes*

Primary analyses focused on remission and included the following.

- Meeting the criteria for depression at end of treatment, as defined by DSM or similar standard diagnostic criteria.
- Less than 50% reduction in depression scale scores at end of treatment.

#### *Secondary outcomes*

- Depression scores as measured on scales such as the Hamilton Depression Rating Scale (HDRS; Hamilton 1960), the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery 1979), the Geriatric Depression Scale (GDS;


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Gompertz 1993), the Beck Depression Inventory (BDI; Beck 1961), and the Hospital Anxiety and Depression Scale (HADS Depression subscale; Zigmond 1983) at end of treatment and at follow-up
- Meeting the criteria for depression at end of follow-up, as defined by DSM or similar standard diagnostic criteria
- Less than 50% reduction in depression scale scores at end of follow-up
- Psychological distress scores, as measured on composite scales such as the General Health Questionnaire (GHQ; Goldberg 1972) at end of treatment
- Anxiety scores, as measured on scales such as the Hamilton Anxiety Scale, the Beck Anxiety Inventory, and the Hospital Anxiety and Depression Scale (HADS Anxiety subscale; Zigmond 1983) at end of treatment
- Cognitive function scores, as measured on scales such as the Mini-Mental State Examination (MMSE; Folstein 1975) at end of treatment
- Activities of daily living scores, as measured on scales such as the Barthel Index (BI; Mahoney 1965) at end of treatment
- Disability scores, as measured on scales such as the Functional Independence Measure (FIM; Deutsch 1997)
- Neurological function scores, as measured on scales such as the National Institutes of Health Stroke Scale (NIHSS; Lyden 2001)
- Disadvantages of treatment recorded as adverse events, grouped by death, all, and leaving the study early (including death)

Participants' reasons for withdrawal from trials were examined as a marker of acceptance.

## Search methods for identification of studies

This review is an update of a previously published Cochrane Review update (2008) (Hackett 2008; Appendix 1). The first review was published in 2004 (Hackett 2004). For this update, we searched all databases from inception until August 2018. We searched for relevant trials in all languages and arranged for translation of trial reports when necessary.

### Specialised Register of Cochrane Stroke

See the methods for the Cochrane Stroke Group Specialised register; the Cochrane Stroke Group Information Specialist searched the Specialised Register of Cochrane Stroke on 13 August 2018.

### Electronic searches

We searched the following bibliographic databases.

- Cochrane Depression Anxiety and Neurosis Trials Register (last searched August 2018).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1), in the Cochrane Library (Appendix 2).
- MEDLINE (OVID): 1966 to August 2018 (Appendix 3).
- Embase (OVID): 1980 to August 2018 (Appendix 4).
- PsycINFO (OVID): 1967 to August 2018 (Appendix 5).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO): 1982 to August 2018 (Appendix 6).
- Science Citation Index - Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), and Arts & Humanities Citation Index (A&HCI) within Web of Science: 2002 to August 2018 (Appendix 7).

Biological Abstracts has now been superseded by ISI Web of Science, which includes the Arts and Humanities Index. Several databases/citation indexes (Applied Science and Technology Plus; Biological Abstracts; BIOSIS Previews; General Science Plus; Dissertations and Theses) listed in Appendix 1 were not used for this update.

### Searching other resources

We searched the following resources using "stroke" or "brain infarction" or "depression" or "low mood" from inception to August 2018.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/en/).

We also searched abstracts and conference proceedings from the following international conferences for relevant studies.

- European Stroke Organisation Conference (2015 to 2018).
- Stroke Society of Australasia Annual Scientific Meetings (2008 to 2018).
- World Stroke Congress (2000 to 2016).
- Asia Pacific Stroke Conference (2011 to 2017).

The full search strategies for other resources are provided in Appendix 8.

#### *Personal communications*

We contacted the study authors to ask for information on ongoing studies or to request additional study data and, in some instances, additional analyses.

#### *Reference lists*

We searched the reference lists of relevant trials, systematic reviews, and 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 treatment or prevention of depression, and writings on stroke and old age.

## Data collection and analysis

### Selection of studies

Two review authors (SA, KC) reviewed all new citations and discarded those that were irrelevant based on the title of the publication and its abstract. When any suggestion was made that an article was possibly relevant, we retrieved the full-length article for further assessment. Two review authors (SA, KC) independently selected the new trials for inclusion in the review from the culled citation list. Potentially relevant Chinese articles were translated by another study author (C-FH). We resolved disagreements by discussion, and MH and AH confirmed the final list and adjudicated any persisting differences of opinion. The selection process is presented in a PRISMA flow diagram (Figure 1). Due to changes in


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the inclusion criteria for this update, records were re-screened from the point of inception. Although we have tried our best to reflect this in the PRISMA flow diagram, it is likely that the numbers will not add up. We listed the included studies under Characteristics of included studies and studies that we ultimately excluded under Characteristics of excluded studies, and we provided the primary reasons for exclusion.


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**Figure 1. Study flow diagram. Eligibility criteria were changed to include non-invasive brain stimulation interventions in this update. The 2015 search was rerun from the point of inception to screen for non-invasive brain stimulation and combination interventions.**

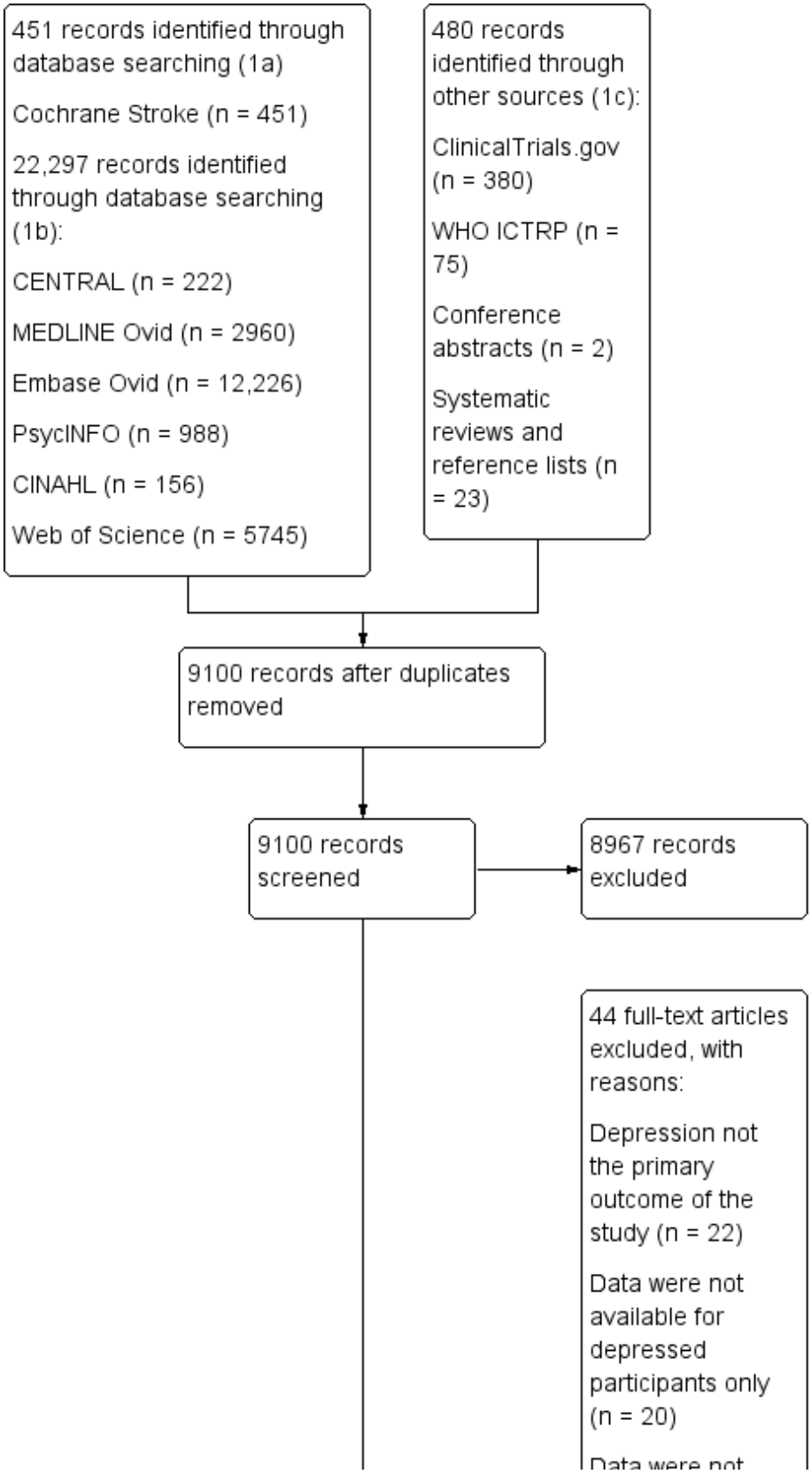



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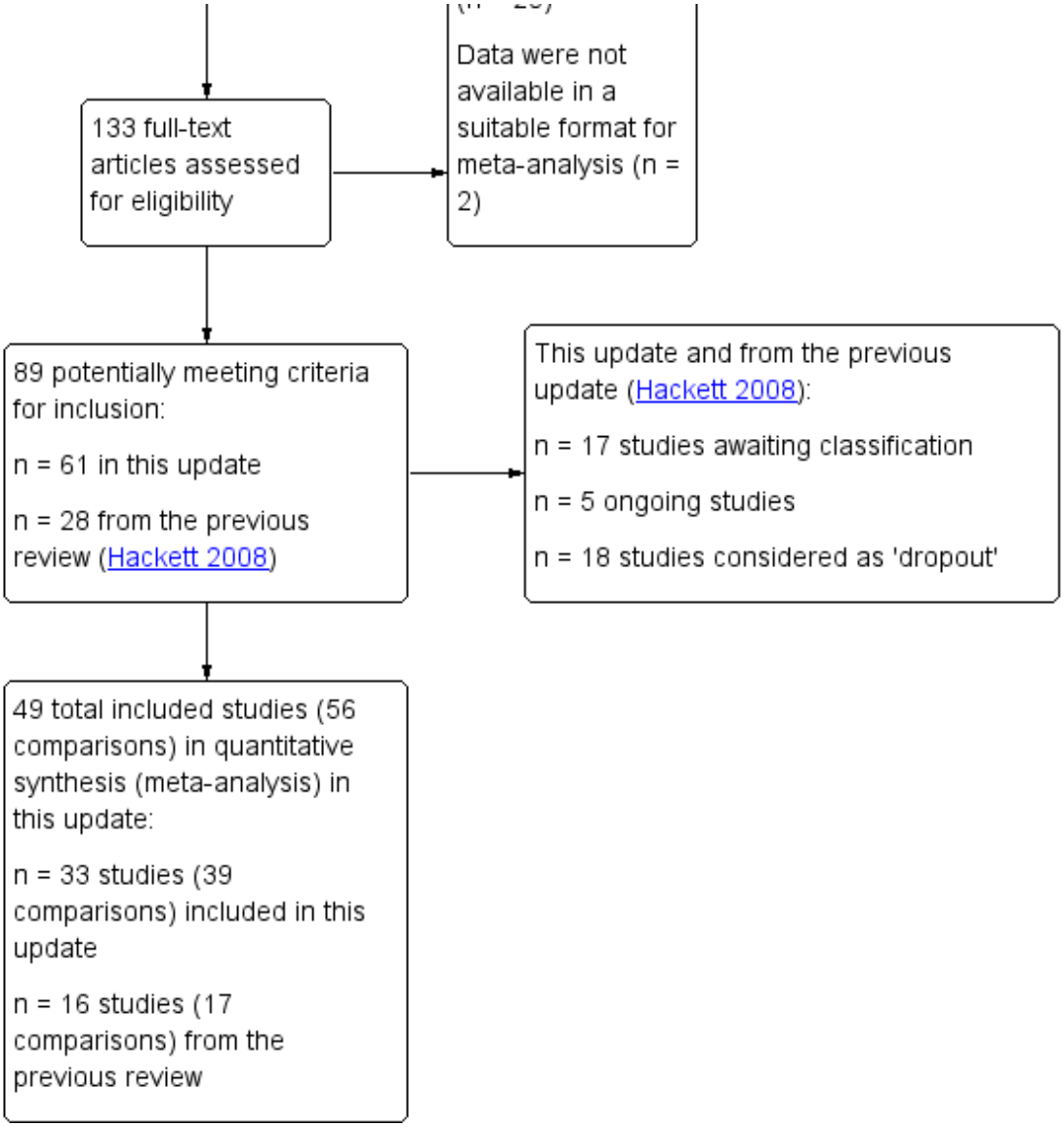
**Figure 1. (Continued)**




**Data extraction and management**

Five review authors (SA, KC, C-FH, HL, MH) independently extracted study characteristics and outcome data from included studies and entered them on specially designed forms. We cross-checked and entered the data into Review Manager 5 (Review Manager 2014). We resolved disagreements by discussion or through consultation with two other review authors (AH or MH). We obtained missing information from the study authors when possible. Information on funding sources is mentioned in the notes sections of the Characteristics of included studies table.

We collected data on:

- the report: author, year, and source of publication;
- the study: sample characteristics, social demography, and definition and criteria used for depression;
- the participants: stroke sequence (first ever vs recurrent), social situation, time elapsed since stroke onset, history of psychiatric illness, current neurological status, current treatment for depression, and 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; and
- the effect size: sample size, nature of outcome, estimate, and standard error on x dy = SD.

To allow for intention-to-treat (ITT) analysis, we sought the data irrespective of adherence and fidelity of the intervention, and regardless of whether participants were subsequently deemed ineligible or were otherwise excluded from treatment or follow-up. When study authors used multiple measures to assess depression,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we extracted data from the measure the study authors stated was used to assess the primary outcome. For measures assessing secondary outcomes, we extracted data from the most commonly used measure. When data for the same trial endpoint were conflicting across multiple publications, we extracted data from the first publication reporting data for that outcome.

We checked all extracted data for agreement between review authors. We obtained missing information from the primary investigators whenever possible. To avoid introducing bias, we obtained this unpublished information in writing, on forms designed for the purpose, and entered it into RevMan.

### Assessment of risk of bias in included studies

Three review authors (SA, KC, C-FH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by consultation with another review author (MH). Although a number of scales have been devised to assess the quality of RCTs, no convincing evidence shows that complex and time-consuming scales are more effective than simple scales (Verhagen 2001). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment: if allocation was performed using opaque envelopes, we also categorised this as 'high risk' as it is not tamper-proof.
- Blinding of participants and personnel: for psychological interventions, we recognise that participants are unlikely to remain blinded; however we also categorised this as 'high risk'.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting: if a published trial had no corresponding published or registered protocol, this was assessed as unclear risk.
- Other bias.

We also provided a quote from the study to justify our judgement in the Risk of bias in included studies table. When considering treatment effects, we have taken into account the risk of bias for studies that contributed to that outcome.

### Measures of treatment effect

#### *Dichotomous data*

For all dichotomous outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) when appropriate, using random-effects analyses.

#### *Continuous data*

For continuous data, if ordinal scale data appeared to be normally distributed, or if the analysis suggested that parametric tests were appropriate, we treated outcome measures as continuous. If at least two studies reported the same outcomes, then we calculated a mean difference (MD) with 95% CI across trials. When different outcome measures were used, we calculated a standardised mean difference (SMD) with 95% CI.

### Unit of analysis issues

We predicted that randomisation would occur at the level of the individual participant in most, if not all, trials. Outcomes are reported at end of treatment and at end of follow-up when data are available. When trials included two or more active intervention arms and only one control arm (placebo, attention control, or usual care), we compared data from each treatment arm with data from the total number of participants in the control arm divided by the number of active intervention arms. Comparisons are presented as separate trials.

### Dealing with missing data

We wrote to the authors of all included, ongoing, and dropout trials to request data that were unavailable or ambiguous in published articles. We also wrote to all pharmaceutical companies known to produce, or having a licence to produce, antidepressants in 2004. We received nine replies identifying no new trials, so we did not repeat this in the 2008 update nor in the current update.

### Assessment of heterogeneity

Clinical and methodological heterogeneity were assessed by examining the study characteristics. We used the $I^2$ statistic to measure heterogeneity among the trials in each analysis (Deeks 2011). If at least two trials reported the same outcomes, we reviewed the data for appropriateness of pooling. We interpreted the amount of heterogeneity as low (0% to 29%), moderate (30% to 49%), substantial (50% to 89%), and considerable (90% to 100%) using $I^2$ values. We reported similarities between interventions, participants, design, and outcomes in the Included studies subsection.

### Assessment of reporting biases

We assessed publication bias by using a funnel plot only if 10 or more trials were included (Higgins 2011). We attempted to avoid language bias by including trials irrespective of language of publication, and we provided translation when needed by native speakers of that language.

In some cases, similarities between trial reports indicated the possibility of multiple publications from the same trial. We contacted study authors to check whether these publications were duplicates. In the absence of a response and explicit cross-referencing, we judged articles to be from the same trial if they met the following criteria: (1) evidence suggested overlapping recruitment sites, trial dates, and grant funding numbers, and (2) similar or identical patient characteristics were reported by trial authors.

### Data synthesis

We analysed data using Review Manager software and pooled data for meta-analysis when studies assessed similar treatments and had similar outcomes (Review Manager 2014). We conducted a meta-analysis using available or calculated MD or SMD for continuous outcomes, and RR for dichotomous outcomes. We included measures of uncertainty in the results, such as 95% CIs and estimates of $I^2$.

#### *'Summary of findings' and certainty of the evidence*

We assessed the certainty of evidence according to GRADE by constructing a 'Summary of findings' table for the outcomes below,


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per comparison, using the GRADEPro tool (GRADEproGDT 2015) (Atkins 2004; Schunemann 2011).

These data were available for comparison: (1) pharmacological interventions versus placebo; (2) one of various forms of non-invasive brain stimulation versus sham stimulation or usual care; (3) one of various forms of psychological therapy versus usual care and/or attention control; (4) pharmacological intervention and various forms of psychological therapy versus pharmacological intervention and usual care and/or attention control (with two comparisons); and (5) non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention and sham stimulation or usual care (with 10 comparisons).

For comparison 1, 'pharmacological intervention versus placebo', we reported certainty of evidence for the following outcomes: meeting study criteria for depression at end of treatment, < 50% reduction in depression scale scores at end of treatment, mean neurological function scores at end of treatment, adverse events related to CNS and gastrointestinal tract and death at end of treatment.

For comparison 2, 'non-invasive brain stimulation versus sham or usual care', we reported certainty of evidence for the following outcomes: mean depression scores at end of treatment, mean depression scores at end of follow-up, mean neurological function scores at end of treatment, and death at end of treatment.

For comparison 3, 'psychological intervention versus usual care or attention control', we reported certainty of evidence for the following outcomes: meeting the study criteria for depression at end of treatment, average change in depression scores between baseline and end of treatment, meeting the study criteria for depression at end of follow-up, death, and leaving the study early (including death) at end of treatment.

For comparison 4, 'pharmacological intervention and a form of psychological therapy (combination) versus pharmacological intervention and usual care or attention control (single)', we reported certainty of evidence for mean depression scores at end of treatment, mean activities of daily living at end of treatment, and death at end of treatment.

For comparison 5, 'non-invasive brain stimulation and pharmacological intervention (combination) versus pharmacological intervention and sham stimulation or usual care (single)', we reported certainty of evidence for the following outcomes: mean depression scores at end of treatment, mean activities of daily living scores at end of treatment, mean neurological function scores at end of treatment, death, and leaving the study early (including death) at end of treatment.

We found no trials for these comparisons: (6) pharmacological intervention and various forms of psychological therapy interventions versus placebo and psychological therapy; (7) pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation; (8) non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control; and (9) non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

### Subgroup analysis and investigation of heterogeneity

We planned to undertake subgroup analyses for all outcomes when feasible to explore the influence of date of publication, sample size, duration of follow-up, treatment type, high (over 20%) number of dropouts, and blinded versus unblinded outcome assessors. If at least two trials reported the same outcomes, we reviewed the data for appropriateness of pooling. If we found definitive evidence of heterogeneity ($I^2$ > 50%), we explored potential reasons for differences by performing subgroup analyses and meta-regression (Normand 1999). If heterogeneity could not be explained, we combined trials using random-effects analyses with cautious interpretation, or we did not combine them at all. When possible, we performed subgroup analyses to examine the impact of treatment type and duration, and of stroke severity.

### Sensitivity analysis

We explored the sensitivity of the combined estimate of individual trials for all outcomes when feasible by leaving one study out if we noted high risk of bias and methodological differences. We then calculated the combined effect of the remaining trials and compared these results with the combined effect based on all trials.

## RESULTS

### Description of studies

#### Results of the search

In total, we identified 23,228 records; of these, we retrieved 22,748 through database searching. We found 480 additional references by searching other resources. After 14,128 duplicates were removed, we screened 9100 titles and abstracts and excluded 8967 irrelevant records. We retrieved full-text reports for the remaining 133 studies. After reading the full texts, we excluded 44 trials as they did not meet the review eligibility criteria. We have provided the primary reasons for exclusions in the Characteristics of excluded studies table and in Figure 1. We identified 10 trials that met the inclusion criteria (Chang 2011; Hadidi 2014; Jorge 2004; Jorge 2008; Kim 2017; Kim 2017a; Kootker 2012; Raffaele 1996; Robinson 2000; Valiengo 2017). However, data were not available for depressed participants only (Chang 2011; Hadidi 2014; Jorge 2004; Jorge 2008; Kim 2017; Kim 2017a; Raffaele 1996; Robinson 2000; Valiengo 2017), or were not in a format suitable for meta-analysis (Kootker 2012). These trials are considered 'dropouts' (Table 1). In the previously published version of this review (Hackett 2008), eight trials met the inclusion criteria but were considered 'dropouts' (Bramanti 1989; Choi-Kwon 2006; Delbari 2011; Downes 1995; Mauri 1988; Meara 1998; Ohtomo 1985; Sun 2000), as outcome data were not available at all (Downes 1995), or outcome data were not available for depressed participants only (Choi-Kwon 2006; Delbari 2011; Ohtomo 1985; Sun 2000), or outcome data were not presented in a format suitable for meta-analysis (Bramanti 1989; Meara 1998; Mauri 1988). See Table 1 for more detailed information on these studies.

We contacted the study authors to ask for information on ongoing studies or to request additional study data and, in some instances, additional analyses. We received responses with additional data regarding seven trials (Andersen 1994; Downes 1995; Fruehwald


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2003; Lincoln 2003; Murray 2002; Reding 1986, Towle 1989). In 2008, we received responses with additional data from the authors of two trials (Lai 2006a; Watkins 2007). We received responses with additional data or information from the authors of seven new trials (Cullen 2018; Fang 2017; Hoffmann 2015; Kerr 2018; Kirkness 2017a; Mitchell 2002; Robinson 2008a).

### Included studies

From the first published version of this review, a total of nine included trials included 671 participants (Andersen 1994; Fruehwald 2003; Lincoln 2003; Lipsey 1984; Murray 2002; Ohtomo 1991; Reding 1986; Towle 1989; Wiart 2000). Seven additional trials (eight comparisons) with 864 participants were included in the 2008 update of this review (Jiang 2001a/Jiang 2001b; Lai 2006a; Ponzio 2001; Rampello 2005; Watkins 2007; Yang 2002; Zhao 2004). Lincoln 2003 compared an active treatment with an attention control (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 another control (standard care). We combined data from the attention control and control groups, and we compared these with data from the treatment group. Jiang 2001a compared two active treatment arms versus a placebo arm. We compared data from both treatment arms against data from half the number of participants in the placebo arm and presented the results as two separate comparisons (Jiang 2001a; Jiang 2001b). More detailed information is provided in Characteristics of included studies.

This present review includes 33 trials (39 comparisons) with 2807 participants. Cao 2009a and Jiang 2014a were parallel RCTs with four arms. We compared data from both treatment arms with their respective control arms and presented the results as separate comparisons (Cao 2009a; Cao 2009b; Jiang 2014a; Jiang 2014b). Gao 2017a and Kirkness 2017a compared two active treatment arms versus a usual care or attention control arm. We compared data from both treatment arms with data from half the number of participants in the usual care or attention control arm and presented the results as separate comparisons (Gao 2017a; Gao 2017b; Kirkness 2017a; Kirkness 2017b). Similarly, Robinson 2008a compared two active treatment arms against a placebo arm. Data from both treatment arms were compared with data from half the number of participants in the placebo arm (Robinson 2008a; Robinson 2008b). Yang 2014a compared two active treatment arms versus a sham non-invasive brain stimulation arm. We compared data from both treatment arms with data from half the number of participants in the sham non-invasive brain stimulation arm (Yang 2014a; Yang 2014b).

#### *Participants*

All trials in this review included men and women. The mean age of participants ranged from 55 to 77.5 years. Most trial authors reported the time since stroke and randomisation into the trial, with the range covering 'within a few days' to 36 months post stroke. Most trials included participants with ischaemic stroke, diagnosed via a combination of standard clinical and computed tomography (CT) criteria. For more detailed information on each included trial, please refer to the Characteristics of included studies table.

#### *Interventions and comparators*

We reported results from the following comparisons: (1) pharmacological intervention versus placebo; (2) non-invasive brain stimulation versus sham non-invasive brain stimulation; (3) one of various forms of psychological therapy versus usual care and/or attention control; (4) pharmacological intervention and one of various forms of psychological therapy versus pharmacological intervention and usual care and/or attention control; and (5) non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention and sham stimulation or usual care. In 18 trials, 20 pharmacological comparisons were assessed against placebo (Andersen 1994; Fruehwald 2003; Gao 2017a; Huang 2002; Jiang 2001a/Jiang 2001b; Kong 2007; Lai 2006a; Li 2008; Lipsey 1984; Murray 2002; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Robinson 2008a/Robinson 2008b; Wang 2005; Wiart 2000; Yang 2002). Seven trials (eight comparisons) reported on non-invasive brain stimulation comparisons versus sham or usual care (Chen 2005a; Gu 2016; Jiang 2014a; Meng 2015; Yang 2013; Yang 2014a;/Yang 2014b; Zheng 2016), and the authors of 15 trials (16 comparisons) assessed various forms of psychological therapy compared to usual care or attention control (Alexopoulos 2012; Cao 2009b; Cullen 2018; Fang 2017; Gao 2017b; Hoffmann 2015; Kerr 2018; Kirkness 2017a/Kirkness 2017b; Lincoln 2003; Mitchell 2002; Thomas 2007; Towle 1989; Wang 2004a; Watkins 2007; Zhao 2004). In two trials (two comparisons), a combination of pharmacological interventions and psychological therapy was assessed against pharmacological intervention and usual care and/or attention control (Cao 2009a; Wang 2005a). In 10 trials (10 comparisons), a combination of non-invasive brain stimulation and pharmacological intervention was compared to pharmacological intervention and sham stimulation or usual care (Du 2005; Fan 2014; Jiang 2014b; Jin 2013; Li 2013; Li 2014; Liu 2015; Lu 2016; Sun 2013; Zhang 2013).

We found no trials for the following comparisons: (6) pharmacological intervention and one of various forms of psychological therapy compared to placebo and psychological therapy; (7) pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation; (8) non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control; and (9) non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

##### Pharmacological interventions

Among the trials of pharmacological interventions, 12 compared an SSRI against placebo (citalopram: Andersen 1994; Gao 2017a; fluoxetine: Fruehwald 2003; Huang 2002; Kong 2007; Li 2008; Wang 2005; Wiart 2000; paroxetine: Lai 2006a; Ponzio 2001; Yang 2002; sertraline: Murray 2002); two trials compared a tricyclic antidepressant against placebo (amitriptyline: Jiang 2001a; nortriptyline: Lipsey 1984); and six trials compared other treatments with antidepressant effects (Deanxit: Jiang 2001b; Aniracetam: Ohtomo 1991; reboxetine: Rampello 2005; trazodone: Reding 1986; nefiracetam: Robinson 2008a; Robinson 2008b). We found no trials of mood stabilisers (e.g. lithium) or benzodiazepines. We found one trial of psychostimulants (e.g. methylphenidate), which was considered a 'dropout' as outcome


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data for those with depression at entry could not be separated from data for those without (Delbari 2011).

#### Non-invasive brain stimulation

Among trials reporting on non-invasive brain stimulation interventions, seven compared rTMS versus sham rTMS or usual care (no changes to antidepressant dosage and medication) (Chen 2005a; Gu 2016; Meng 2015; Yang 2013; Yang 2014a; Yang 2014b; Zheng 2016). In only one trial, TMS was compared with usual care (Jiang 2014a). Two trials compared high-frequency rTMS versus sham or usual care (Yang 2013; Yang 2014a), and one trial compared low-frequency rTMS versus sham stimulation or usual care (Yang 2014b). We found no trials of ECT. Any future trials will be included but analysed separately.

#### Psychological therapy

Forms of psychological therapy included structured cognitive-behavioural therapy delivered by trained psychologists or nurses (Gao 2017b; Hoffmann 2015; Lincoln 2003; Mitchell 2002; Thomas 2007); motivational interviewing (MI) delivered by nurses or non-clinical psychologists (Kerr 2018; Watkins 2007); psychosocial therapy delivered by psychosocial nurse practitioner therapists in person or via telephone (Fang 2017; Kirkness 2017a; Kirkness 2017b); group psychotherapy (Cao 2009b); and psychotherapy with an ecosystem aspect (Alexopoulos 2012); treatments focused on psychological support (Wang 2004a), problem-solving therapy with counselling delivered by social workers (Towle 1989), and a supportive psychological intervention including education delivered by special personnel (Cullen 2018; Zhao 2004).

#### Combination therapy

In two trials, a combination of psychotherapy and an SSRI was compared with an SSRI alone (fluoxetine: Cao 2009a; paroxetine: Wang 2005a). In six trials, rTMS and an SSRI were compared with an SSRI (fluoxetine: Du 2005; Li 2014; Zhang 2013; citalopram: Liu 2015; sertraline: Jiang 2014b; Jin 2013). In two trials, rTMS and an SNRI were compared with an SNRI alone (duloxetine: Fan 2014; Lu 2016). In one trial, rTMS and another antidepressant medication were compared with an antidepressant alone (mirtazapine: Li 2013). Only one trial compared rTMS and a combination of antipsychoactive agents and tricyclic antidepressants (flupenthixol and melitracen: named Deanxit) versus Deanxit alone (Sun 2013).

### *Outcomes*

#### Primary outcome - depression

In 14 trials (15 comparisons), outcome data for meeting the study criteria for depression at end of treatment were assessed and reported (Alexopoulos 2012; Andersen 1994; Fang 2017; Fruehwald 2003; Kirkness 2017a/Kirkness 2017b; Lincoln 2003; Lipsey 1984; Mitchell 2002; Murray 2002; Ohtomo 1991; Ponzio 2001; Watkins 2007; Yang 2002; Zhao 2004). For the outcome less than 50% reduction in depression scale scores at end of treatment, six trials contributed data (Andersen 1994; Lai 2006a; Li 2008; Murray 2002; Wiart 2000; Yang 2002).

#### Secondary outcomes

A variety of additional outcomes were assessed in each trial. Several trials assessed and reported outcome data for depression scores (Alexopoulos 2012; Andersen 1994; Cao 2009b; Chen 2005a; Cullen 2018; Fruehwald 2003; Gu 2016; Hoffmann 2015; Huang 2002; Jiang 2001a; Jiang 2001b; Kerr 2018; Kong 2007; Lai 2006a; Li 2008; Lincoln 2003; Lipsey 1984; Mitchell 2002; Murray 2002; Rampello 2005; Robinson 2008a; Robinson 2008b; Thomas 2007; Wang 2004a; Wiart 2000; Yang 2013; Yang 2014a; Yang 2014b; Zhao 2004), psychological distress scores (Lincoln 2003; Watkins 2007), anxiety scores (Cullen 2018; Fang 2017; Hoffmann 2015; Kerr 2018; Wang 2005a), cognitive function scores (Du 2005; Gao 2017a; Gao 2017b; Wang 2005; Wiart 2000), activities of daily living scores (Cao 2009a; Cao 2009b; Du 2005; Fan 2014; Gao 2017a; Gao 2017b; Hoffmann 2015; Kerr 2018; Kirkness 2017a; Kirkness 2017b; Kong 2007; Li 2008; Li 2014; Lincoln 2003; Meng 2015; Mitchell 2002; Yang 2013), disability scores (Alexopoulos 2012; Chen 2005a; Fruehwald 2003; Lu 2016; Sun 2013; Wang 2004a; Watkins 2007; Wiart 2000), and neurological function scores (Huang 2002; Jiang 2001a; Jiang 2001b; Jiang 2014a; Jiang 2014b; Jin 2013; Kong 2007; Liu 2015; Meng 2015; Zheng 2016). In 24 trials (28 comparisons), study authors reported having systematically measured and reported adverse events (Alexopoulos 2012; Andersen 1994; Du 2005; Fang 2017; Fruehwald 2003; Gao 2017a/Gao 2017b; Gu 2016; Huang 2002; Jiang 2001a/Jiang 2001b; Jiang 2014a/Jiang 2014b; Li 2008; Lincoln 2003; Lipsey 1984; Liu 2015; Meng 2015; Mitchell 2002; Murray 2002; Ponzio 2001; Robinson 2008a/Robinson 2008b; Thomas 2007; Towle 1989; Wang 2005a; Watkins 2007; Wiart 2000). Adverse event data often were not collected, were not reported, or were reported poorly.

## Excluded studies

We excluded a total of 44 trials at the full-text review stage for a variety of reasons, including (1) depression not the primary outcome of the study (n = 22); (2) data not available for depressed participants only (n = 20); or (3) data not available in a suitable format for meta-analysis (n = 2). See Characteristics of excluded studies.

### *Ongoing studies*

Five trials are ongoing (Kirkevold 2018: psychological therapy; NCT03056287: non-invasive brain stimulation; Tang 2017: non-invasive brain stimulation; Thomas 2016: psychological therapy; Xu 2016: pharmacological intervention).

### *Studies awaiting classification*

From the previously published version of this review, four trials are listed as awaiting classification (Evans 1985; Hanspal 2007; Katz 1998; Pearson 2005). We were unable to obtain more information or outcome data from these trials despite multiple attempts to contact the study authors. In the present review, 13 trials (17 comparisons) are awaiting classification (Chen 2002a/Chen 2002b; Ding 2005; Finkenzeller 2009; He 2003; He 2005; Huang 2005; Latow 1983; Lee 2005; Liu 2010; Razazian 2016; Tang 2002; Wang 2015; Yan 2010a/Yan 2010b/Yan 2010c/Yan 2010d). We were unable to obtain more information or outcome data for three of these despite multiple attempts to contact the study authors (He 2003; Latow 1983; Lee 2005). For two trials (three comparisons), we were unsure if depression was the primary outcome (Chen 2002a/Chen 2002b; Razazian 2016). In eight trials (11 comparisons), no information was provided for the psychotherapy component of the intervention to help us determine if it meets our review criteria (Ding 2005; Finkenzeller 2009; He 2005; Huang 2005; Liu 2010; Tang 2002; Wang 2015; Yan 2010a/Yan 2010b/Yan 2010c/Yan 2010d).


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***Dropout studies***

From the previously published review, eight trials met the inclusion criteria for this review (Bramanti 1989; Choi-Kwon 2006; Delbari 2011; Downes 1995; Mauri 1988; Meara 1998; Ohtomo 1985; Sun 2000). However, no outcome data were available in one trial (unpublished data only: Downes 1995); in others, data were not presented on depressed participants at baseline (Choi-Kwon 2006; Delbari 2011; Ohtomo 1985; Sun 2000), or data were not presented in a suitable format for inclusion in the meta-analysis (Bramanti 1989; Mauri 1988; Meara 1998).

In this review, 10 additional trials met the inclusion criteria (Chang 2011; Hadidi 2014; Jorge 2004; Jorge 2008; Kim 2017; Kim 2017a; Kootker 2012; Raffaele 1996; Robinson 2000; Valiengo 2017). However, data were not presented on depressed participants only at baseline (Chang 2011; Hadidi 2014; Jorge 2004; Kim 2017; Kim 2017a; Raffaele 1996; Robinson 2000), or data were not presented in a suitable format (Kootker 2012; Valiengo 2017), or we were unable to verify if any participants had a diagnosis of stroke or if there were duplicate data from another trial (Jorge 2008). We considered these trials as 'dropouts' and have provided more detailed information in Table 1.

## Risk of bias in included studies

We present a graphical summary of risk of bias assessments performed by review authors for the included trials in Figure 2, based on the seven risk of bias domains. Figure 3 provides a summary of risk of bias for each included trial. We have provided the reasons for judgements in the Risk of bias in included studies tables.

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

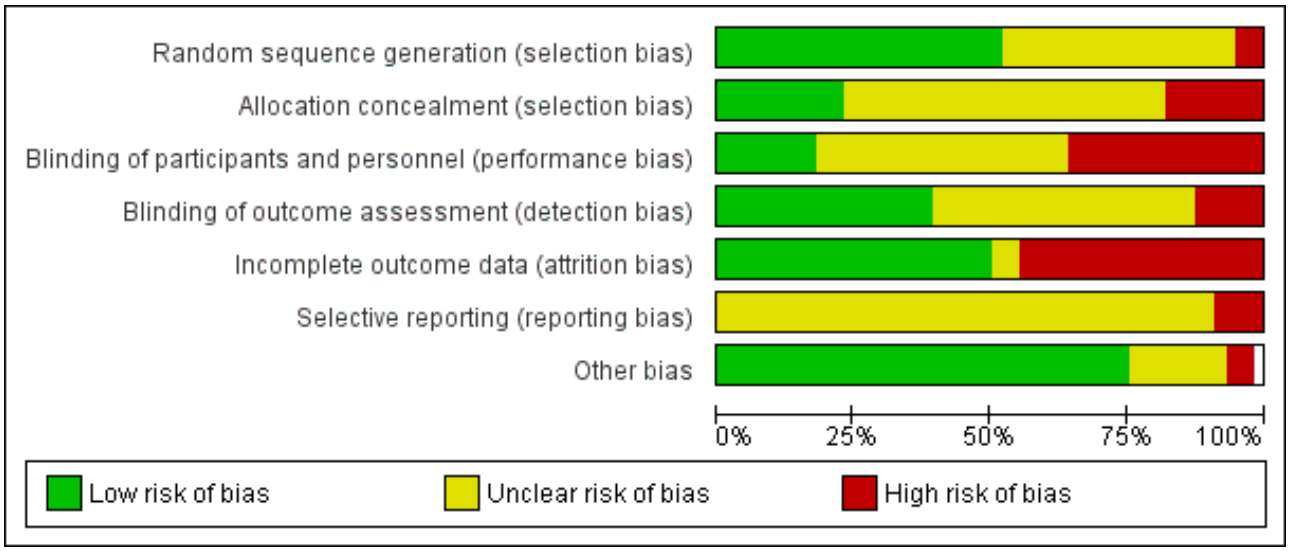



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**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

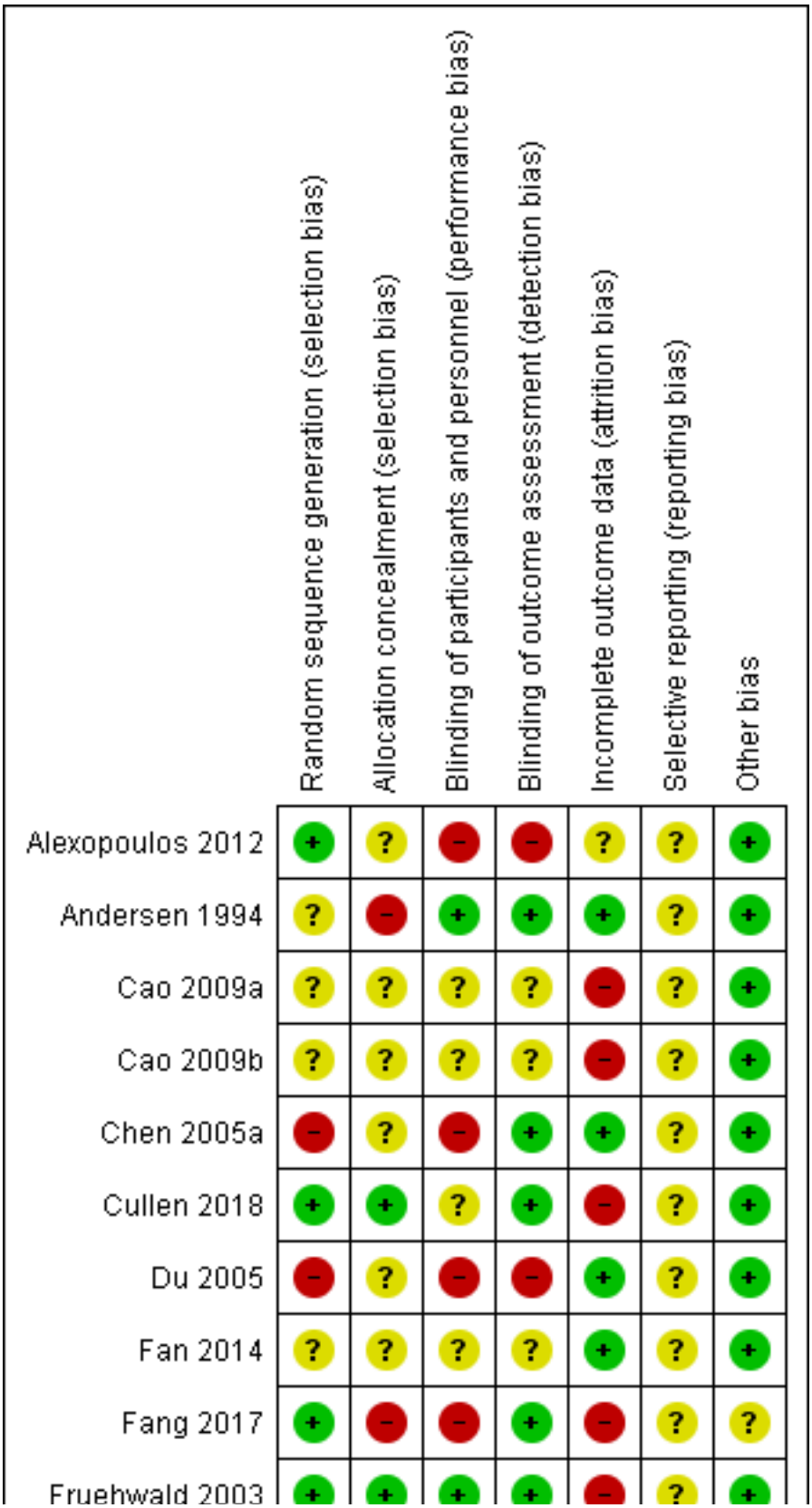



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**Figure 3. (Continued)**

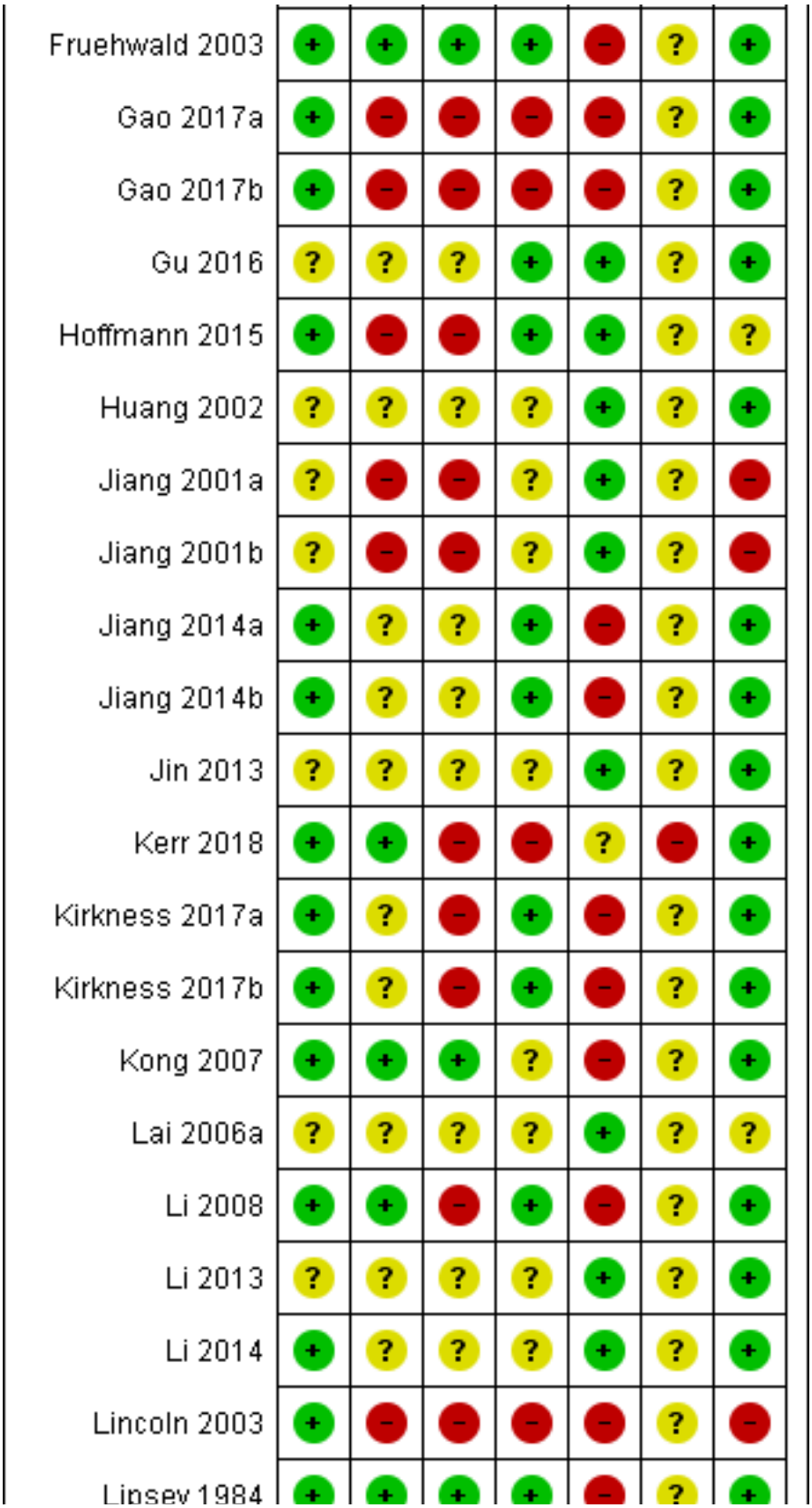



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**Figure 3. (Continued)**

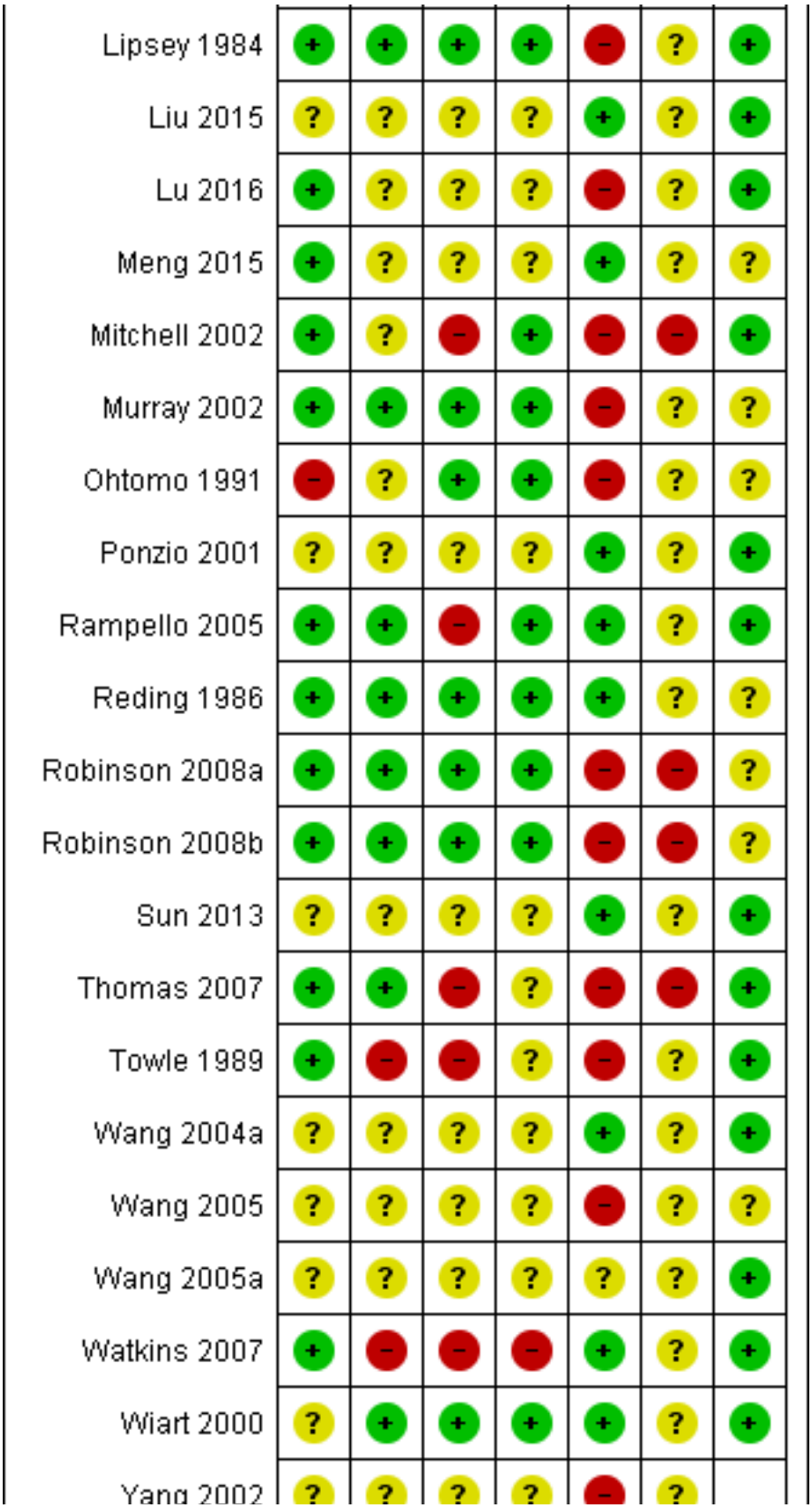



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**Figure 3. (Continued)**

### Allocation

The randomisation sequence was appropriately generated in 25 trials (29 comparisons); thus we rated then as low risk (Alexopoulos 2012; Cullen 2018; Fang 2017; Fruehwald 2003; Gao 2017a/Gao 2017b; Hoffmann 2015; Jiang 2014a/Jiang 2014b; Kerr 2018; Kirkness 2017a/Kirkness 2017b; Kong 2007; Li 2008; Li 2014; Lincoln 2003; Lipsey 1984; Lu 2016; Meng 2015; Mitchell 2002; Murray 2002; Rampello 2005; Reding 1986; Robinson 2008a/Robinson 2008b; Thomas 2007; Towle 1989; Watkins 2007; Zhang 2013). However, 21 trials (24 comparisons) did not describe their method of sequence generation, and so we rated them as unclear risk (Andersen 1994; Cao 2009a/Cao 2009b; Fan 2014; Gu 2016; Huang 2002; Jiang 2001a/Jiang 2001b; Jin 2013; Lai 2006a; Li 2013; Liu 2015; Ponzio 2001; Sun 2013; Wang 2004a; Wang 2005; Wang 2005a; Wiart 2000; Yang 2002; Yang 2013; Yang 2014a/Yang 2014b; Zhao 2004; Zheng 2016). We rated three trials as high risk, as generation of sequence was controlled by the investigators (Ohtomo 1991), or the method was drawing lots (Chen 2005a; Du 2005), which could be manipulated.

We rated 12 trials (13 comparisons) as low risk, as an appropriately generated and clearly concealed allocation procedure was used in the study (Cullen 2018; Fruehwald 2003; Kerr 2018; Kong 2007; Li 2008; Lipsey 1984; Murray 2002; Rampello 2005; Reding 1986; Robinson 2008a/Robinson 2008b; Thomas 2007; Wiart 2000). Twenty-nine trials (33 comparisons) did not describe adequate concealment allocation, and we rated them as unclear risk (Alexopoulos 2012; Cao 2009a/Cao 2009b; Chen 2005a; Du 2005; Fan 2014; Gu 2016; Huang 2002; Jiang 2014a/Jiang 2014b; Jin 2013; Kirkness 2017a/Kirkness 2017b; Lai 2006a; Li 2013; Li 2014; Liu 2015; Lu 2016; Meng 2015; Mitchell 2002; Ohtomo 1991; Ponzio 2001; Sun 2013; Wang 2004a; Wang 2005; Wang 2005a; Yang 2002; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zhao 2004; Zheng 2016). We rated eight trials (10 comparisons) as high risk for allocation concealment, as they used sealed opaque envelopes, which could be tampered with (Andersen 1994; Fang 2017; Gao 2017a/Gao 2017b; Hoffmann 2015; Jiang 2001a/Jiang 2001b; Lincoln 2003; Towle 1989; Watkins 2007) .

### Blinding

The authors of nine trials (10 comparisons) reported that participants and personnel were blinded to the treatment allocation, and so we rated these trials as low risk for performance bias (Andersen 1994; Fruehwald 2003; Kong 2007; Lipsey 1984; Murray 2002; Ohtomo 1991; Reding 1986; Robinson 2008a/Robinson 2008b; Wiart 2000). We rated 22 trials (25 comparisons) as unclear risk, as they did not provide information about blinding of participants and personnel (Cao 2009a/Cao 2009b; Cullen 2018; Fan 2014; Gu 2016; Huang 2002; Jiang 2014a/Jiang 2014b; Jin 2013; Lai 2006a; Li 2013; Li 2014; Liu 2015; Lu 2016; Ponzio 2001; Sun 2013; Wang 2004a; Wang 2005; Wang 2005a; Yang 2002; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zheng 2016). We rated 15 trials (18 comparisons) as high risk for performance bias, as participants or personnel were not blinded to treatment allocation (Alexopoulos 2012; Chen 2005a; Du 2005; Fang 2017; Gao 2017a/Gao 2017b; Hoffmann 2015; Jiang 2001a/Jiang 2001b; Kerr 2018; Kirkness 2017a/Kirkness 2017b; Li 2008; Lincoln 2003; Rampello 2005; Towle 1989; Watkins 2007; Zhao 2004).

We rated 19 trials (24 comparisons) as low risk for detection bias, as outcome assessors were blinded to treatment allocation (Andersen 1994; Chen 2005a; Cullen 2018; Fang 2017; Fruehwald 2003; Gu 2016; Hoffmann 2015; Jiang 2014a/Jiang 2014b; Kirkness 2017a/Kirkness 2017b; Li 2008; Lipsey 1984; Mitchell 2002; Murray 2002; Ohtomo 1991; Rampello 2005; Reding 1986; Robinson 2008a/Robinson 2008b; Wiart 2000; Zhao 2004). Twenty-four trials (27 comparisons) did not provide information about blinding of outcome assessors, and we rated them as unclear risk of detection bias (Cao 2009a/Cao 2009b; Fan 2014; Huang 2002; Jin 2013; Kong 2007; Jiang 2001a/Jiang 2001b; Lai 2006a; Li 2013; Li 2014; Liu 2015; Lu 2016; Meng 2015; Ponzio 2001; Sun 2013; Thomas 2007; Towle 1989; Wang 2004a; Wang 2005; Wang 2005a; Yang 2002; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zheng 2016). We rated six trials (seven comparisons) as high risk because they did not use blinded outcome assessment (Alexopoulos 2012; Du 2005; Gao 2017a/Gao 2017b; Kerr 2018; Lincoln 2003; Watkins 2007).


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### Incomplete outcome data

We rated 26 trials (29 comparisons) as low risk, as they provided ITT analyses (Andersen 1994; Chen 2005a; Du 2005; Fan 2014; Hoffmann 2015; Huang 2002; Jiang 2001a/Jiang 2001b; Jin 2013; Lai 2006a; Li 2013; Li 2014; Liu 2015; Meng 2015; Ponzio 2001; Rampello 2005; Reding 1986; Sun 2013; Wang 2004a; Wang 2005; Watkins 2007; Wiart 2000; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zhao 2004; Zheng 2016). We rated 18 trials (22 comparisons) as high risk for attrition bias, as they reported per-protocol analyses only (Cullen 2018; Fang 2017; Fruehwald 2003; Gao 2017a/Gao 2017b; Jiang 2014a/Jiang 2014b; Kirkness 2017a/Kirkness 2017b; Kong 2007; Li 2008; Lincoln 2003; Lipsey 1984; Lu 2016; Mitchell 2002; Murray 2002; Ohtomo 1991; Robinson 2008a/Robinson 2008b; Thomas 2007; Towle 1989; Yang 2002). The method of analysis was unclear in four trials (five comparisons) (Alexopoulos 2012; Cao 2009a/Cao 2009b; Kerr 2018; Wang 2005a).

### Selective reporting

We rated 45 trials (51 comparisons) as unclear risk for reporting bias, as no trial protocol was available to compare a priori outcomes versus those reported in publications (Alexopoulos 2012; Andersen 1994; Cao 2009a/Cao 2009b; Chen 2005a; Cullen 2018; Du 2005; Fan 2014; Fang 2017; Fruehwald 2003; Gao 2017a/Gao 2017b; Gu 2016; Hoffmann 2015; Huang 2002; Jiang 2001a/Jiang 2001b; Jiang 2014a/Jiang 2014b; Jin 2013; Kirkness 2017a/Kirkness 2017b; Kong 2007; Lai 2006a; Li 2008; Li 2013; Li 2014; Lincoln 2003; Lipsey 1984; Liu 2015; Lu 2016; Meng 2015; Murray 2002; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Sun 2013; Towle 1989; Wang 2004a; Wang 2005; Wang 2005a; Watkins 2007; Wiart 2000; Yang 2002; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zhao 2004; Zheng 2016). We rated four trials (five comparisons) as high risk, as one or two outcomes mentioned in the study protocol or trial registry information page were not reported in the primary results publication (Kerr 2018; Mitchell 2002; Robinson 2008a/Robinson 2008b; Thomas 2007).

### Other potential sources of bias

We rated 38 trials (44 comparisons) as low risk for other bias, as baseline demographics and depression scores were balanced between groups (Alexopoulos 2012; Andersen 1994; Cao 2009a/Cao 2009b; Chen 2005a; Cullen 2018; Du 2005; Fan 2014; Fruehwald 2003; Gao 2017a/Gao 2017b; Gu 2016; Huang 2002; Jiang 2001a/Jiang 2001b; Jiang 2014a/Jiang 2014b; Jin 2013; Kerr 2018; Kirkness 2017a/Kirkness 2017b; Kong 2007; Li 2008; Li 2013; Li 2014; Lipsey 1984; Liu 2015; Lu 2016; Mitchell 2002; Ponzio 2001; Rampello 2005; Sun 2013; Thomas 2007; Towle 1989; Wang 2004a; Wang 2005a; Watkins 2007; Wiart 2000; Yang 2013; Yang 2014a/Yang 2014b; Zhang 2013; Zhao 2004; Zheng 2016). We rated 10 trials (11 comparisons) as unclear, as no information about baseline demographics and depression scores between groups was provided (Fang 2017; Hoffmann 2015; Lai 2006a; Meng 2015; Murray 2002; Ohtomo 1991; Reding 1986; Robinson 2008a/Robinson 2008b; Wang 2005; Yang 2002). We rated two trials (three comparisons) as high risk, as baseline demographic or depression scores were uneven between groups (Jiang 2001a/Jiang 2001b; Lincoln 2003).

## Effects of interventions

See: **Summary of findings for the main comparison** Pharmacological intervention compared to placebo for treating depression after stroke; **Summary of findings 2** Non-invasive brain stimulation compared to sham non-invasive brain stimulation and/or usual care for treating depression after stroke; **Summary of findings 3** Psychological therapy compared to usual care and/or attention control for treating depression after stroke; **Summary of findings 4** Pharmacological intervention and a form of psychotherapy (combination) compared to pharmacological intervention and usual care or attention control (single) for treating depression after stroke; **Summary of findings 5** Non-invasive brain stimulation and pharmacological intervention (combination) compared to pharmacological intervention and sham stimulation or usual care (single) for treating depression after stroke

Overall, we included 3342 participants in this review. In view of the large number and heterogeneous nature of the outcome measures (multiple measures often used for the same endpoint with no primary measure stated) and the reporting of results, we considered it inappropriate to pool outcome data for many endpoints. For details of all comparisons made for the trials with outcome data, refer to the Data and analyses section.

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; and Summary of findings 5 for comparisons.

### Primary outcomes

#### *Depression (remission)*

##### Meeting study criteria for depression at end of treatment

Eight trials (eight comparisons) on pharmacological interventions reported on the outcome meeting study criteria for depression at end of treatment (Andersen 1994; Fruehwald 2003; Lipsey 1984; Murray 2002; Ohtomo 1991; Ponzio 2001; Wang 2005; Yang 2002). We observed treatment effects favouring pharmacological interventions compared to placebo (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.55 to 0.88, 1025 participants, very low-certainty evidence; Analysis 1.1). However, substantial heterogeneity ($I^2$ = 68%) and wide confidence intervals were evident across individual trials.

No trials of non-invasive brain stimulation alone assessed this outcome (Analysis 2.1).

Five trials (six comparisons) of psychological therapy reported on the outcome meeting study criteria for depression at end of treatment and demonstrated an effect favouring psychological therapy over usual care and/or attention control (RR 0.77, 95% CI 0.62 to 0.95; 6 RCTs; 521 participants; very low-certainty evidence) (Alexopoulos 2012; Fang 2017; Kirkness 2017a/Kirkness 2017b; Mitchell 2002; Watkins 2007). We observed low heterogeneity ($I^2$ = 36%) and wide confidence intervals (Analysis 3.1).

No trials of combination therapies assessed this outcome (Analysis 4.1; Analysis 5.1).

##### Less than 50% reduction in depression scale scores

Six trials (six comparisons) of pharmacological interventions reported on this outcome (Andersen 1994; Lai 2006a; Li 2008; Murray 2002; Wiart 2000; Yang 2002). We observed treatment effects favouring pharmacological therapy among those who received a pharmacological intervention compared with placebo (RR 0.47, 95% CI 0.32 to 0.69; 6 RCTs; 511 participants; very low-certainty


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evidence). We observed substantial heterogeneity ($I^2$ = 66%) and wide confidence intervals (Analysis 1.2).

We did not perform a meta-analysis for the comparison non-invasive brain stimulation versus sham non-invasive brain stimulation or usual care (Analysis 2.2).

No trials of psychological interventions versus usual care and/or attention control and pharmacological intervention and psychological therapy (combination) versus pharmacological intervention and usual care or attention control (single) assessed this outcome (Analysis 3.2; Analysis 4.2).

We did not perform a meta-analysis for the comparison non-invasive brain stimulation and pharmacological intervention (combination) versus pharmacological intervention and sham stimulation or usual care (single), as only one trial reported data on this outcome for each comparison (Analysis 5.2).

### Secondary outcomes

#### *Depression scores*

##### Average change in scores between baseline and end of treatment

We did not perform a meta-analysis on this outcome for the comparison pharmacological interventions versus placebo (Analysis 1.3), due to the heterogenous nature of the outcome measures and single trials using multiple measures for this outcome without specifying a primary outcome measure. Two trials (three comparisons) found an effect favouring psychological therapy over usual care and/or attention control (mean difference (MD) -6.20, 95% CI -8.24 to -4.16; 3 RCTs; 189 participants; very low-certainty evidence; Analysis 3.3) (Kirkness 2017a/Kirkness 2017b; Mitchell 2002).

##### Mean scores at end of treatment

We did not perform a meta-analysis on this outcome for the comparison pharmacological interventions versus placebo due to the heterogenous nature of the outcome measures (Analysis 1.4).

Seven trials (eight comparisons) demonstrated an effect favouring non-invasive brain stimulation over sham or usual care at end of treatment (MD -6.63, 95% CI -9.71 to -3.55; 8 RCTs; 495 participants; very low-certainty evidence) (Chen 2005a; Gu 2016; Jiang 2014a; Meng 2015; Yang 2013; Yang 2014a/Yang 2014b; Zheng 2016). However, considerable heterogeneity ($I^2$ = 99%) and very wide confidence intervals (Analysis 2.3 subgroup 2.3.1) are evident.

We did not perform a meta-analysis on the outcome for comparison of psychological therapy versus usual care and/or attention control (Analysis 3.4) due to the heterogenous nature of the outcome measures.

We also observed a beneficial effect for combination therapy (pharmaceutical intervention and psychological therapy) compared to pharmaceutical intervention alone at end of treatment (MD -1.53, 95% CI -2.10 to -0.96; 2 RCTs; 198 participants; very low-certainty evidence; Analysis 4.3 subgroup 4.3.1). Heterogeneity was substantial ($I^2$ = 87%) and confidence intervals were very wide. We also observed this effect among those who received a combination of non-invasive brain stimulation and pharmacological intervention in comparison to those who received pharmacological intervention alone at end of treatment (MD -4.09, 95% CI -5.61 to -2.57; 9 RCTs; 685 participants; very low-certainty evidence; Analysis 5.3 subgroup 5.3.1). Heterogeneity was substantial ($I^2$ = 88%) and confidence intervals were very wide.

##### Mean scores at end of follow-up

Three trials (three comparisons) of non-invasive brain stimulation addressed the outcome of mean depression scores at end of follow-up and revealed an effect favouring non-invasive brain stimulation over sham or usual care (MD -2.60, 95% CI -3.3 to -1.87; 3 RCTs; 170 participants; very low-certainty evidence; Analysis 2.4 subgroup 2.4.1) (Gu 2016; Meng 2015; Yang 2013). However, confidence intervals were very wide.

We did not perform a meta-analysis for the comparison non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention alone, as only one trial reported data on this outcome (Analysis 5.4 subgroup 5.4.1).

##### Meeting study criteria for depression at end of follow-up

Two trials (three comparisons) of psychological therapy assessed this outcome and showed no statistically significant effects for those who received psychological therapy compared to usual care and/or attention control (RR 0.85, 95% CI 0.59 to 1.21; 3 RCTs; 201 participants; very low-certainty evidence; $I^2$ = 11%; Analysis 3.5, subgroup 3.5.1) (Kirkness 2017a/Kirkness 2017b; Mitchell 2002).

#### *Psychological distress scores*

No significant effect was observed in those who received psychological therapy compared to usual care and/or attention control on the outcome average change in scores between baseline and end of treatment (MD -0.21, 95% CI -1.89 to 1.48; 2 RCTs; 377 participants; very low-certainty evidence) (Lincoln 2003; Watkins 2007). Nor did we observe a significant effect on mean psychological distress scores at end of treatment (MD -0.43, 95% CI -2.17 to 1.31; 2 RCTs; 377 participants; very low-certainty evidence). See Analysis 3.8 subgroup 3.8.1 and Analysis 3.9 subgroup 3.9.1.

#### *Anxiety scores*

##### Mean scores at end of treatment

We did not perform a meta-analysis on this outcome for comparison of psychological therapy versus usual care and/or attention control due to the heterogenous nature of the outcome measures and single trials using multiple measures for this outcome without specifying a primary outcome measure (Analysis 3.11).

##### Mean scores at end of follow-up

We did not perform a meta-analysis on this outcome for comparison: psychological therapy versus usual care and/or attention control due to the heterogenous nature of the outcome measures and single trials using multiple measures for this outcome without specifying a primary outcome measure (Analysis 3.12).

#### *Cognitive function scores*

We did not perform a meta-analysis, as only one trial reported data for this outcome (Analysis 1.6; Analysis 1.7; Analysis 5.5).


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### *Activities of daily living (ADL) scores*

#### Average change in scores between baseline and end of treatment

Two trials (two comparisons) revealed that pharmacological intervention compared to placebo had no significant effect on the average change in scores between baseline and end of treatment (MD -8.00, 95% CI -24.18 to 8.18; 2 RCTs; 256 participants; very low-certainty evidence) (Ponzio 2001; Reding 1986) (Analysis 1.8 subgroup 1.8.1). Similarly, two trials (two comparisons) also showed that psychological therapy compared to usual care and/or attention control had no significant effect on the average change in scores between baseline and end of treatment (SMD -0.03, 95% CI -0.24 to 0.18; 2 RCTs; 377 participants; very low-certainty evidence; Analysis 3.13) (Lincoln 2003; Watkins 2007).

#### Mean scores at end of treatment

Three trials of pharmacological interventions (three comparisons) found no significant effect on mean ADL scores at end of treatment compared with placebo (MD 3.14, 95% CI -0.97 to 7.26; 3 RCTs; 316 participants; very low-certainty evidence; Analysis 1.9 subgroup 1.9.1) (Gao 2017a; Kong 2007; Li 2008). Two trials (two comparisons) demonstrated no effect among those who received non-invasive brain stimulation compared to sham or usual care (SMD 1.84, 95% CI -1.40 to 5.08; 2 RCTs; 208 participants; very low-certainty evidence; Analysis 2.5) (Jiang 2014a; Meng 2015). However, we observed considerable heterogeneity ($I^2$ = 99%) and very wide confidence intervals.

We did not perform a meta-analysis on this outcome for comparison: psychological therapy versus usual care and/or attention control (Analysis 3.14), due to the heterogenous nature of the outcome measures and single trials using multiple measures for this outcome without specifying a primary outcome measure.

Two trials (two comparisons) found that a combination of pharmacological intervention and psychological therapy had no effect on mean ADL scores compared to a single pharmacological intervention at end of treatment (MD 11.83, 95% CI 0.27 to 23.40; 2 RCTs; 198 participants; very low-certainty evidence; Analysis 4.5 subgroup 4.5.1) (Cao 2009a; Wang 2005a). Similarly, five trials (five comparisons) showed that combination therapy (non-invasive brain stimulation and pharmacological intervention) had no effect compared to pharmacological intervention alone (single) (SMD 2.03, 95% CI 1.21 to 2.85; 5 RCTs; 403 participants; very low-certainty evidence; Analysis 5.6) (Du 2005; Fan 2014; Jiang 2014b; Li 2013; Li 2014). However, the two comparisons showed considerable heterogeneity ($I^2$ = 94% and $I^2$ = 91%) and very wide confidence intervals.

#### Mean scores at end of follow-up

We did not perform a meta-analysis, as only one trial reported data on this outcome (Analysis 3.15).

### *Disability scores*

Two trials (two comparisons) found that psychological therapy had no effect on mean disability scores at end of treatment compared to usual care and/or attention control (SMD -0.16, 95% CI -0.48 to 0.17; 2 RCTs; 162 participants; very low-certainty evidence; Analysis 3.16) (Alexopoulos 2012; Gao 2017b). Although two trials (two comparisons) reported that non-invasive brain stimulation and pharmacological intervention (combination) had an effect on mean disability scores at end of treatment compared to pharmacological intervention alone (MD -10.02, 95% CI -20.14 to 0.11; 2 RCTs; 180 participants; very low-certainty evidence; Analysis 5.7 subgroup 5.7.1) (Lu 2016; Sun 2013).

### *Neurological function scores*

#### Mean scores at end of treatment

Four trials (four comparisons) showed that pharmacological interventions had an effect on mean scores at end of treatment compared to placebo (SMD -0.95, 95% CI -1.44 to -0.45; 4 RCTs; 304 participants; very low-certainty evidence; Analysis 1.13) (Huang 2002; Jiang 2001a; Kong 2007; Wang 2005). Heterogeneity was substantial ($I^2$ = 75%) and confidence intervals were very wide. Similarly, we observed an effect among those who received non-invasive brain stimulation compared to sham or usual care (SMD -2.21, 95% CI -3.32 to -1.09; 3 RCTs; 290 participants; very low-certainty evidence; Analysis 2.7) (Meng 2015; Jiang 2014a; Zheng 2016). However, we noted considerable heterogeneity ($I^2$ = 93%) and wide confidence intervals.

We did not perform a meta-analysis for this comparison: pharmacological intervention and psychological therapy versus pharmacological intervention alone (Analysis 4.6 subgroup 4.6.1), as only one trial reported data on this outcome.

In contrast, four trials (four comparisons) found that a combination of non-invasive brain stimulation and pharmacological intervention had an effect on mean scores at end of treatment compared to pharmacological intervention alone (MD -2.78, 95% CI -4.13 to -1.44; 4 RCTs; 280 participants; very low-certainty evidence; Analysis 5.8 subgroup 5.8.1) (Jiang 2014b; Jin 2013; Li 2013; Liu 2015). Heterogeneity was substantial ($I^2$ = 82%) and confidence intervals were very wide.

### *Adverse events: death*

Nine trials (nine comparisons) found that pharmacological intervention had no effect on adverse events compared to placebo: death (RR 0.64, 95% CI 0.20 to 2.07; 9 RCTs; 848 participants; very low-certainty evidence; Analysis 1.14 subgroup 1.14.1) (Andersen 1994; Fruehwald 2003; Gao 2017a; Huang 2002; Li 2008; Lipsey 1984; Murray 2002; Ponzio 2001; Wiart 2000). Although no heterogeneity was observed ($I^2$ = 0%), confidence intervals were very wide.

Two trials (two comparisons) reported that non-invasive brain stimulation resulted in no deaths (Gu 2016; Jiang 2001a) (Analysis 2.8 subgroup 2.8.1).

Eight trials (eight comparisons) found that psychological therapy had no effect on adverse events compared to usual care or attention control: death (RR 0.65, 95% CI 0.26 to 1.66; 8 RCTs; 831 participants; very low-certainty evidence; Analysis 3.17 subgroup 3.17.1) (Alexopoulos 2012; Fang 2017; Gao 2017b; Lincoln 2003; Mitchell 2002; Thomas 2007; Towle 1989; Watkins 2007). We observed no heterogeneity ($I^2$ = 0%) but confidence intervals were very wide.

Three trials (three comparisons) reported that a combination of non-invasive brain stimulation and pharmacological intervention resulted in no deaths compared to pharmacological intervention and sham stimulation or usual care (Du 2005; Jiang 2014b; Liu 2015)) (Analysis 5.9 subgroup 5.9.1).


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***Adverse events: all***

Significant evidence of harm was demonstrated among adverse events, in particular, CNS effects (RR 1.55, 95% CI 1.12 to 2.15; 5 RCTs; 488 participants; very low-certainty evidence; $I^2$ = 31%) (Andersen 1994; Lipsey 1984; Murray 2002; Ponzio 2001; Wiart 2000), along with gastrointestinal effects (RR 1.62, 95% CI 1.19 to 2.19; 4 RCTs; 473 participants; very low-certainty evidence) (Li 2008; Murray 2002; Ponzio 2001; Wiart 2000), among those who received pharmacological interventions compared with placebo (see Analysis 1.15 subgroup 1.15.1 and 1.15.5). We observed no heterogeneity ($I^2$ = 0%), but the confidence intervals were very wide.

Two trials (two comparisons) reported that non-invasive brain stimulation resulted in no other adverse events - not listed above (e.g. dysuria, eye discomfort; Analysis 2.9) (Gu 2016; Jiang 2014a).

Four trials (four comparisons) found that psychological therapy resulted in no significant adverse events (recurrent stroke - RR 5.0, 95% CI 0.24 to 103.12; 1 RCT; 254 participants; vascular events - RR 0.71, 95% CI 0.23 to 2.19; 1 RCT; 254 participants; very low-certainty evidence), nor other events - not listed above (e.g. too ill) (RR 1.02, 95% CI 0.15 to 6.81; 2 RCTs; 206 participants; very low-certainty evidence). See Analysis 3.18 (Mitchell 2002; Thomas 2007; Towle 1989; Watkins 2007).

Two trials (two comparisons) found that a combination of non-invasive brain stimulation and pharmacological intervention resulted in no significant adverse events (other events - not listed above, e.g. insomnia, discomfort, headache) (RR 7.0, 95% CI 0.38 to 129.93; 2 RCTs; 120 participants; very low-certainty evidence). See Analysis 5.10 (Du 2005; Jiang 2014b).

***Adverse events: leaving the study early (including death)***

Twelve trials (13 pharmacological comparisons) reported on this outcome (Andersen 1994; Fruehwald 2003; Gao 2017a; Huang 2002; Kong 2007; Li 2008; Lipsey 1984; Murray 2002; Ponzio 2001; Robinson 2008a/Robinson 2008b; Wang 2005; Wiart 2000). Pharmacological interventions had no effect on the proportion of participants leaving the study early (including death) compared to placebo (RR 1.07, 95% CI 0.82 to 1.39; 13 RCTs; 1165 participants; very low-certainty evidence; Analysis 1.16 subgroup 1.16.1). Although we observed no heterogeneity ($I^2$ = 0%), confidence intervals were very wide.

Seven trials (eight comparisons) revealed that psychological therapy had no effect on the proportion of participants leaving the study early (including death) compared to usual care and/or attention control (RR 0.83, 95% CI 0.42 to 1.63; 8 RCTs; 784 participants; very low-certainty evidence; Analysis 3.19 subgroup 3.19.1) (Alexopoulos 2012; Gao 2017b; Kirkness 2017a/Kirkness 2017b; Lincoln 2003; Mitchell 2002; Towle 1989; Watkins 2007). Although we observed no heterogeneity ($I^2$ = 0%), confidence intervals were very wide.

Four combination therapy trials (rTMS and pharmacological interventions) (four comparisons) reported on this outcome. A combination of rTMS and pharmacological interventions had no effect on the proportion of people leaving the study early (including death) compared to pharmacological intervention alone (RR 1.33, 95% CI 0.32 to 5.58; 4 RCTs; 300 participants; very low-certainty evidence) (Du 2005; Jiang 2014b; Liu 2015; Lu 2016). See Analysis 5.11 subgroup 5.11.1. We observed no heterogeneity ($I^2$ = 0%), but confidence intervals were very wide.

## DISCUSSION

### Summary of main results

In this review update, we included 49 trials (56 comparisons) involving 3342 participants that met our criteria. The large increase in the number of included trials is partially explained by expansion of the types of included interventions. This is the first time we have included other (in addition to electroconvulsive therapy (ECT)) non-invasive brain stimulation interventions and combination interventions.

Data were available for these comparisons: (1) pharmacological interventions versus placebo; (2) one of various forms of non-invasive brain stimulation versus sham stimulation or usual care; (3) one of various forms of psychological therapy versus usual care and/or attention control; (4) pharmacological intervention and various forms of psychological therapy versus pharmacological intervention and usual care and/or attention control (with two comparisons); and (5) non-invasive brain stimulation and pharmacological intervention versus pharmacological intervention and sham stimulation or usual care (with 10 comparisons).

Comparison 1. Comparing pharmacological intervention to placebo, we found very low-certainty pooled evidence suggesting benefit in treating depression to remission and reducing depressive symptom scores on mood rating scales, along with evidence of harm (more central nervous system and gastrointestinal adverse events). These results are largely unchanged from previous versions of this review. For pharmacological trials, a key requirement is that a therapeutic dose of the medication must be achieved for an adequate period of time. Guidelines from 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 pharmacological trials probably were not given for an adequate length of time to show maximal or sustained response. Therefore, we are unable to comment on the long-term effects of antidepressant therapy, or to provide information on the most appropriate duration or dose of treatment; nor can we say if one group of antidepressants is more efficacious or provide stopping rules for antidepressant therapy in this group.

Comparison 2. Comparing non-invasive brain stimulation to usual care or sham stimulation, we found very low-certainty pooled evidence that repetitive transcranial magnetic stimulation (rTMS) reduces depressive symptom scores at end of treatment and after follow-up, off treatment. No reported data were related to remission. No adverse events were reported. We did not include this endpoint in previous versions of this review. The duration of treatment in these trials was short, ranging from one to four weeks. The impact of many different facets of interventions such as rTMS (including electrode placement, number of sessions, or particular frequencies on outcomes) is not within the scope of this review.

Comparison 3. Comparing psychological therapy to usual care or attention control, we found very low-certainty pooled evidence of benefit in treating depression to remission at end of treatment,


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but this benefit was not sustained to the end of follow-up off treatment. We did not pool data related to changes in depression symptom scores due to use of multiple measures across and within studies with no a priori primary outcome measure identified. Pooled evidence for adverse events included benefit and harm. These results are different from findings of previous versions of this review, which demonstrated no treatment effects. For psychological therapy trials, good evidence shows that efficacy is linked to delivery of adequate exposure to the intervention. This means that therapists should be trained and supervised in the therapy they are delivering, and should use a standardised, pre-specified framework for therapy. To achieve this in psychological therapy trials, therapy is determined with use of a manual, and research therapists are trained and supervised in 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 psychological therapy trials should adhere to these standard psychological therapy research guidelines if there is to be any probability of demonstrating consistency and response.

Comparison 4. Comparing combined pharmacological intervention and psychological therapy to pharmacological intervention plus usual care or attention control, we found very low-certainty pooled evidence of benefit in reducing depressive symptom scores on mood rating scales. No reported data were related to remission. We did not include this endpoint in previous versions of this review.

Comparison 5. Comparing non-invasive brain stimulation and pharmacological intervention to usual care or sham stimulation and pharmacological intervention, we found very low-certainty pooled evidence of benefit in reducing depressive symptom scores on mood rating scales. No reported data were related to remission. Pooled evidence for adverse events included benefit and harm. We did not include this endpoint in previous versions of this review.

We found no trials for these comparisons: (6) pharmacological intervention and various forms of psychological therapy interventions compared with placebo and psychological therapy; (7) pharmacological intervention and non-invasive brain stimulation versus placebo plus non-invasive brain stimulation; (8) non-invasive brain stimulation and one of various forms of psychological therapy versus non-invasive brain stimulation plus usual care and/or attention control; and (9) non-invasive brain stimulation and one of various forms of psychological therapy versus sham brain stimulation or usual care plus psychological therapy.

Evidence demonstrating benefit must continue to 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 in the methods used to diagnose depression, lack of an a priori measurable endpoint, and high risk of bias in many trials. Of particular concern is the evidence of harm (more adverse events) given the small number of trials in which adverse events were systematically recorded and reported, making reliable assessment of the benefits and risks of treatments impossible.

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 participants with narrow demographic and clinical characteristics, in particular, they excluded people with communication problems, cognitive loss, or previous psychiatric illness. This reinforces a common criticism of depression research - that 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 on the basis of such criteria (Turner-Stokes 2003). Given the older age of most people with stroke and the frequent presence of neurological impairments, aphasia, and comorbid medical conditions, the fact that up to half of all survivors of stroke are excluded limits the external validity (generalisability) of the results. 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 comorbidities and other characteristics. Such exclusions may be justifiable for trials of psychological therapy, in which participants are required to actively participate in therapy by talking, but the exclusions seem inappropriate for 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 subarachnoid haemorrhage, it could be argued that this form of stroke should be examined separately.

Lack of a consistent method to diagnose depression at trial entry and outcomes 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 have stated whether the primary goal of therapy was remission (no longer meeting the baseline criteria for depression), response (> 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. 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 for the treating physician. These problems with outcome assessment were further confounded by frequent use of multiple scales and selective reporting of findings between and within trials. Any one scale was used across only eight trials at most, and significantly different cut-points were used to determine depression at entry and at trial end. Given the practical difficulties and high costs of conducting psychiatric interviews in clinical trials, it seems appropriate to adopt a pragmatic approach to assess depression on the basis of a validated mood questionnaire or structured interview. It is hoped that 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


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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 dropout rates were high in several trials. Additionally, blinding of investigators and outcome assessors was seldom stated.

## Overall completeness and applicability of evidence

The present review included 49 trials (56 comparisons) with 3342 participants. Data were available for 20 pharmacological comparisons, eight non-invasive brain stimulation comparisons, 16 psychological therapy comparisons, and 11 combination therapy trials. Overall, consistent methods used to diagnose depression were lacking, and we considered it inappropriate to pool outcome data for many endpoints. The accuracy of the findings of this systematic review and meta-analysis must be considered in light of the basic methodological limitations described in the Risk of bias in included studies table. Eighteen trials are considered dropouts, 21 trials are awaiting classification, and at least five ongoing trials may contribute further evidence to future updates of this review.

## Quality of the evidence

We rated the certainty of evidence for all comparisons by using the five GRADE considerations (study limitations, consistency of effect, indirectness, imprecision, and publication bias; Schunemann 2011). We created a 'Summary of findings' table for each comparison. Certainty assessment was very low.

### Limitations in study design or execution

For the comparison of pharmacological interventions versus placebo, we downgraded the certainty of evidence by two points for the following outcomes: meeting study criteria for depression at end of treatment, less than 50% reduction in depression scale scores, mean neurological function scores at end of treatment, and adverse events - death at end of treatment, all CNS events, and gastrointestinal events - as we rated several studies as having high or unclear risk for multiple risk of bias domains (Summary of findings for the main comparison).

For the comparison of non-invasive brain stimulation versus sham, we downgraded the certainty of evidence by two points for the following outcomes: mean depression scores at end of treatment, mean depression scores at end of follow-up, and mean neurological function scores at end of treatment, as we rated several studies as having high or unclear risk for multiple risk of bias domains (Summary of findings 2).

For the comparison of psychological therapy versus usual care and/or attention control, we downgraded the certainty of evidence by two points for the following outcomes: meeting study criteria for depression at end of treatment, average change in depression scores between baseline and end of treatment, meeting study criteria for depression at end of follow-up, and adverse events - death at end of treatment and leaving the study early - as we rated several studies as having high or unclear risk for multiple risk of bias domains (Summary of findings 3).

For the comparison of pharmacological interventions and psychological therapy (combination) versus pharmacological intervention and usual care and/or attention control (single), we downgraded the certainty of evidence by two points for the following outcomes: mean depression scores at end of treatment and mean activities of daily living scores at end of treatment, as we rated two studies as having unclear risk for multiple risk of bias domains, related to allocation concealment and blinding of participants, personnel, and outcome assessors (Summary of findings 4).

For the comparison of non-invasive brain stimulation and pharmacological intervention (combination) versus pharmacological intervention with sham or usual care (single), we downgraded by two points the certainty of evidence for mean depression scores, mean activities of daily living scores at end of treatment, and leaving the study early, as we rated the study as having high risk for multiple risk of bias domains, related to blinding of participants, personnel, and outcome assessors (Summary of findings 5).

### Inconsistency of results

For the comparison of pharmacological interventions versus placebo, we downgraded by two points the certainty of evidence for the following outcomes: meeting study criteria for depression, less than 50% reduction in depression scale scores, and mean neurological function scores at end of treatment, as we observed substantial heterogeneity (50% to 89%). We also downgraded the certainty of evidence by one point for gastrointestinal events, as we observed moderate heterogeneity (30% to 49%) (Summary of findings for the main comparison).

For the comparison of non-invasive brain stimulation versus sham, we downgraded the certainty of evidence by two points for mean depression scores and neurological function scores at end of treatment due to considerable heterogeneity observed (90% to 100%) (Summary of findings 2).

For the comparison of pharmacological interventions and psychological therapy (combination) versus pharmacological intervention and usual care and/or attention control (single), we downgraded by two points the certainty of evidence for mean depression scores at end of treatment due to substantial heterogeneity (50% to 89%), and by two points for mean activities of daily living scores at end of treatment for considerable heterogeneity (90% to 100%) observed (Summary of findings 4).

For the comparison of non-invasive brain stimulation and pharmacological intervention (combination) versus pharmacological intervention with sham or usual care (single), we downgraded by one point the certainty of evidence for mean depression scores and mean neurological function scores at end of treatment due to substantial heterogeneity (50% to 89%) observed. We also downgraded by two points the certainty of evidence for mean activities of daily living scores at end of treatment as considerable heterogeneity (90% to 100%) was observed (Summary of findings 5).

### Indirectness of evidence

All included trials addressed the main review questions (PICO). Thus, we did not downgrade any outcomes for indirectness of evidence (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).


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**Imprecision**

For the comparison of pharmacological interventions versus placebo, we downgraded the certainty of evidence by one point for the following outcomes: meeting study criteria for depression and less than 50% reduction in depression scale scores at end of treatment, as the confidence intervals were wide. We also downgraded by two points the certainty of evidence for mean neurological scores and adverse events - death, CNS events, and gastrointestinal events at end of treatment, as the confidence intervals were very wide (Summary of findings for the main comparison).

For the comparison of non-invasive brain stimulation versus sham, we downgraded the certainty of evidence by two points for the following outcomes: mean depression scores at end of treatment and mean depression scores at end of follow-up, as the confidence intervals were very wide. We also downgraded by one point the certainty of evidence for mean neurological function scores at end of treatment, as the confidence intervals were wide (Summary of findings 2).

For the comparison of psychological therapy versus usual care and/or attention control, we downgraded the certainty of evidence by one point for meeting criteria for depression at end of treatment, as the confidence intervals were wide. We also downgraded by two points the certainty of evidence for the following outcomes: average change in depression scores between baseline and end of treatment, meeting study criteria for depression at end of follow-up, and adverse events - death at end of treatment and leaving the study early - as the confidence intervals were very wide (Summary of findings 3).

For the comparison of pharmacological interventions and psychological therapy (combination) versus pharmacological intervention and usual care and/or attention control (single), we downgraded the certainty of evidence by two points for mean depression scores and activities of daily living scores at end of treatment, as the confidence intervals were very wide (Summary of findings 4).

For the comparison of non-invasive brain stimulation and pharmacological intervention (combination) versus pharmacological intervention with sham or usual care (single), we downgraded the certainty of evidence by two points for the following outcomes: mean depression scores, mean activities of daily living scores, and mean neurological function scores at end of treatment and leaving the study early, as the confidence intervals were very wide (Summary of findings 5).

**Publication bias**

We assessed publication bias using funnel plots for the outcome meeting study criteria for depression at end of treatment for pharmaceutical interventions versus placebo; Figure 4 shows no evidence of publication bias for this outcome. We did not assess publication bias using funnel plots for the other outcomes in each comparison due to the small number of studies (< 10 studies) contributing to the analysis. Therefore, we did not downgrade the certainty of evidence for publication bias for any outcomes per comparison (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).


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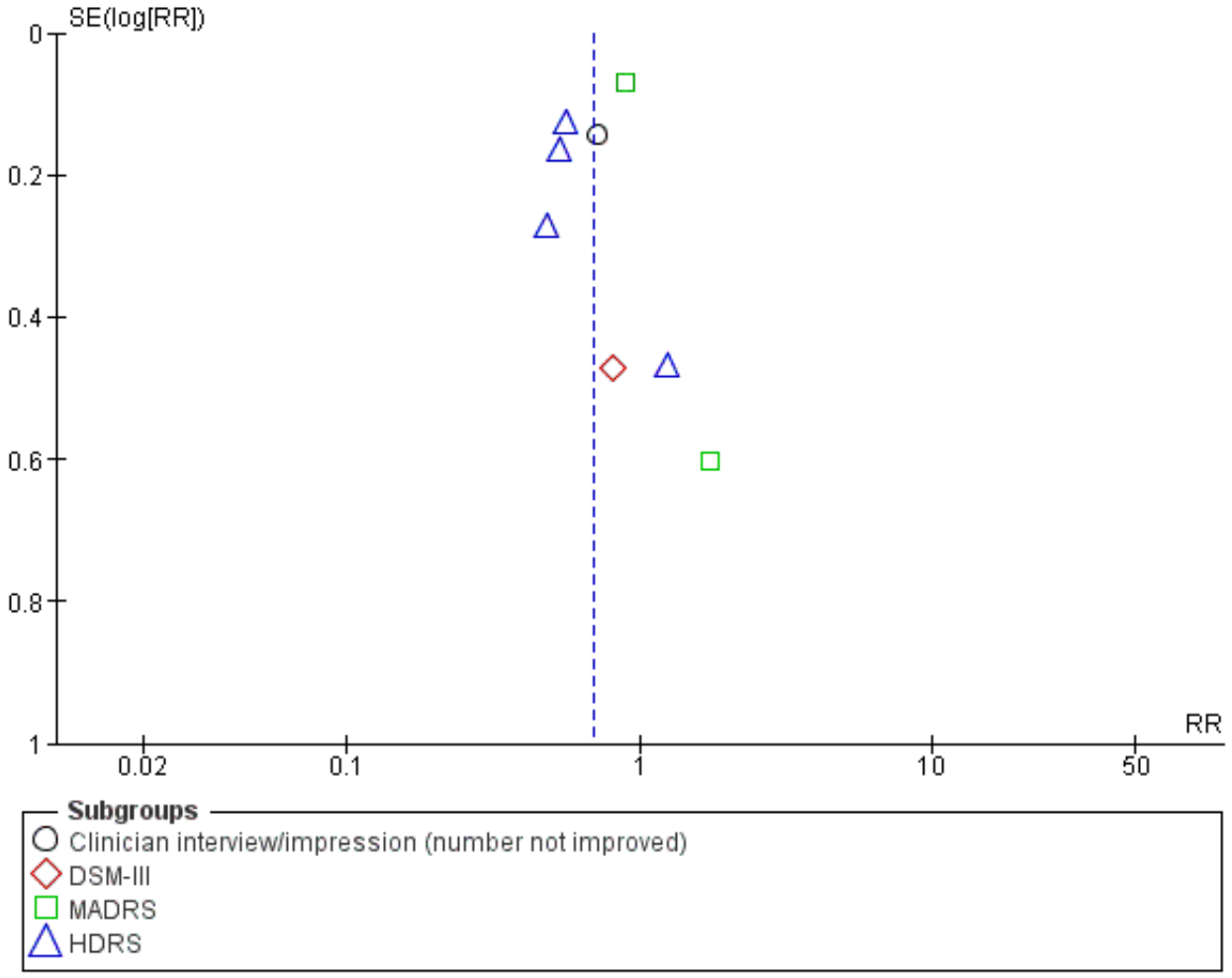
**Figure 4. Funnel plot of comparison: 1 Pharmacological interventions versus placebo, outcome: 1.1 Depression: meeting study criteria for depression at end of treatment.**




## Potential biases in the review process

### Strengths and weaknesses of this review

This review has rigorously adhered to Cochrane methods for performing systematic reviews. During the review process, we tried to avoid and minimise any biases. We undertook extensive searches of databases and additional resources. We did not apply any language restrictions during the search process. Thus, we believe that we have identified and included in this review all potentially relevant trials. We arranged for any relevant and non-relevant non-English full-text trials to be translated into English, to finalise the eligibility process. Furthermore, at least two review authors independently extracted and managed the data.

The main weaknesses of this review are the heterogeneous nature of the outcome measures and the frequent use of multiple scales between and within trials. Inadequate reporting of some trials has led us to rate some of these trials across categories as having unclear risk of bias, with an overall rating of 'very low' certainty of evidence.

## Agreements and disagreements with other studies or reviews

To date, no other systematic reviews have been as comprehensive as this current review.

We found one other systematic review comparing effects of pharmacotherapy versus placebo in the stroke population (Chen 2006). Although this review appears similar, there are important differences in the inclusion criteria. We included trials of people with depression on recruitment and excluded trials with participants who were not depressed at recruitment (included in Hackett 2008a; update pending). Other reviews included trials of people with and without diagnosed depression at recruitment. This limits our ability to directly compare results. One network meta-analysis comparing pharmacotherapy to placebo in people with a diagnosis of major depressive disorder (but not stroke) also found low-quality pooled evidence of benefit of pharmacotherapy in treating depression to remission (Cipriani 2018). Many trials in that review also provided inadequate information about randomisation and allocation concealment, which restricts interpretation of their results. This indicates that limitations in study design in pharmacotherapy trials are not limited to stroke.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One systematic review compared effects of rTMS with sham rTMS and a combination of rTMS and pharmacotherapy versus usual care or sham rTMS and pharmacotherapy in treating depression after stroke (Shen 2017). Those review authors included 22 trials (24 comparisons), of which 13 trials (15 comparisons) are also included in our review (Chen 2005a; Fan 2014; Jiang 2014a; Jiang 2014b; Jin 2013; Li 2013; Li 2014; Liu 2015; Lu 2016; Meng 2015; Yang 2013; Yang 2014a; Yang 2014b; Zhang 2013; Zheng 2016), and two trials (three comparisons) are awaiting classification (Liu 2010; Yan 2010a/Yan 2010b). Seven of the trials included in Shen 2017 did not meet our review criteria for the type of intervention. These trials compared rTMS and pharmacotherapy versus pharmacotherapy alone (with no sham rTMS or usual care). We did not include any additional trials in our review. This review also found low-quality pooled evidence that rTMS and a combination of rTMS and pharmacotherapy reduced depressive symptom scores at end of treatment and after follow-up. However, these findings must also be considered in light of the same limitations in study design and heterogeneity. Another systematic review compared effects of non-invasive brain stimulation (which includes rTMS and transcranial direct current stimulation (tDCS)) versus sham stimulation or usual care (Bucur 2018). Review authors included seven studies (case studies and randomised controlled trials (RCTs)), of which one trial is also included in our review (Gu 2016), and two trials are considered 'dropouts', as outcome data were not reported grouped by depressed/non-depressed participants at baseline (Jorge 2004; Valiengo 2017). Review authors did not perform a meta-analysis and only narratively described the included studies.

One systematic review reported on effects of cognitive-behavioural therapy (CBT) in treating depression after stroke. These review authors included 23 trials, two of which are included in our review (Gao 2017b; Lincoln 2003), and one is considered a 'dropout' as the outcome data (reported median and interquartile ratio (IQR)) were not suitable for pooling (Kootker 2012). The 20 trials that are not included in our review were conducted and published in China, and none were identified by our search strategy, nor were they accessible during this update. We will endeavour to locate, translate, and assess these 20 trials in time for the next update of this review.

Identification of ongoing studies and those awaiting classification indicates that this is an area of stroke research for which further evidence will evolve over the short and longer term.

## AUTHORS' CONCLUSIONS

### Implications for practice

Evidence from trials in people with stroke tentatively supports the use of prescription antidepressants or psychological therapy to treat depression, but this must be considered in light of evidence of an associated increase in harm. Antidepressants may produce a remission or a response in terms of lower scores on mood rating scales but may also increase adverse events. Psychological therapy does not appear to have the same associated risks. Any use of pharmacological agents in people with persistent depressive disorder after stroke would require caution, as little is known about the risks, especially of seizures, falls, delirium, and interaction with other medications.

### Implications for research

We recommend that further research is needed in this area. Future trials investigating effects of pharmacological, psychological, and non-invasive brain stimulation interventions, alone and in combination, for treatment of depression in people after stroke should:

- 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, inclusion of patients with dysphasia, and subarachnoid haemorrhage (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 most stroke survivors;
- provide treatment for sufficient duration and follow-up, so that rates of relapse or maintenance of remission can be assessed;
- carefully specify and monitor psychological interventions;
- describe interventions in sufficient detail to allow their replication;
- include careful, prospective assessment and complete reporting of adverse events;
- define a priori an unambiguous, measurable primary endpoint; and
- 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]*

### Alexopoulos 2012

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Treatment arm:**ecosystem focused therapy (EFT)<br><br>**Control arm:** attention control |
| Participants | **Geographical location:** USA<br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br><br>**Method of stroke diagnosis:** not reported<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) aged 60 years or older; (2) had an ischaemic, embolic, or haemorrhagic stroke; (3) diagnosis of unipolar major depression by DSM-IV<br><br>**Exclusion criteria:** (1) moderately severe dementia (MMSE score < 20); (2) greater than moderate aphasia (NIHSS best language > 1); (3) expectation to be discharged to a nursing home; (4) psychotic depression (by DSM-IV); (5) suicidal intent or plan; (6) inability to speak English<br><br>**Depression criteria:** structured clinical interview for DSM-IV-TR and PHQ-9 cut-off score ≥ 10<br><br>**Total number randomised in this trial:** 24<br><br>**Number randomised to treatment group:** 12 (50% men, mean age 72 years, SD 7)<br><br>**Number randomised to control group:** 12 (58% men, mean age 69 years, SD 10) |


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**Alexopoulos 2012** *(Continued)*

| | |
|---|---|
| | **Total number included in the final analysis:** 24<br><br>**Number included in treatment group for final analysis:** 12 (50% men, mean age 72 years, SD 7)<br><br>**Number included in control group for final analysis:** 12 (58% men, mean age 69 years, SD 10) |
| Interventions | **Treatment:** 12 weekly 45-minute personalised sessions of EFT were offered. Treatment was designed to increase patient participation in rehabilitation and social activities, focusing on adherence, problem-solving, goal-setting, and co-ordination of care<br><br>**Administered by:** therapist trained in EFT using manuals; qualification of therapist not stated<br><br>**Attention control:** 12 weekly 45-minute sessions of Education on Stroke and Depression (ESD)<br>**Administered by:** therapist trained in ESD using manuals; qualification of therapist not stated<br><br>**Supervision:** 3 practice cases of EFT and ESD were supervised; qualifications of the supervisor not stated<br><br>**Intervention fidelity:** all EFT and ESD sessions were audio-taped and rated by reviewers who were not members of the research team, using specially devised EFT and ESD fidelity scales (5 grades: 1 = poor, 5 = excellent). Mean EFT scores ranged from 4.0 to 4.4; mean ESD scores ranged from 4.6 to 4.9, indicating good intervention fidelity for both arms<br><br>**Duration:** 12 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depressive symptoms measured using the HDRS<br><br>**Secondary outcomes**<br><br>• Remission of depression (HDRS < 10)<br>• Disability measured using the WHODAS-II |
| Notes | **Author contact:** emailed study authors to ask how missing data were handled and to ask for information on sample size calculation 19 November 2018 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "the subjects were randomly assigned to EFT or ESD using random numbers" (p. 1055) |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "four therapists were trained and offered both EFT and ESD…" (p. 1056)<br><br>**Comment:** due to the nature of the trial, it was not possible to mask participants, therapists, or researchers to the treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Quote:** "…..the raters could not be blinded to the treatment condition, although they were unaware of the study hypotheses" (p. 1058) |


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**Alexopoulos 2012** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | **Comment:** in the intervention arm, 2 died, 1 LTF was reported; in the control arm, 1 discontinued treatment. Analysis includes all patients (ITT), but how missing data were handled was not reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes were reported. No trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no statistically significant differences in demographic characteristics, age of depression between EFT- and ESD-treated participants |

**Andersen 1994**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** citalopram (SSRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Denmark<br>**Setting:** mixed outpatient and inpatient<br><br>**Stroke criteria:** ischaemic stroke and primary intracerebral haemorrhage<br><br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br><br>**Time since stroke:** 2 to 52 weeks (average time 12 weeks)<br><br>**Inclusion criteria:** (1) had stroke 2 to 52 weeks before randomisation<br><br>**Exclusion criteria:** (1) patients with subarachnoid haemorrhage or Binswanger's disease; (2) with previous degenerative or expansive neurological disease (such as multiple sclerosis, amyotrophic lateral sclerosis, tumour, and hydrocephalus); (3) with history of psychiatric illness (except depression more than 1 year earlier); (4) decreased consciousness; (5) dementia; (6) aphasia to such a degree that they could not explain themselves or gave conflicting verbal and non-verbal signals<br><br>**Depression criteria:** HDRS score > 12 (score transformed to appropriate DSM-III-R criteria)<br><br>**Total number randomised in this trial:** 66<br><br>**Number randomised to treatment group:** 33 (36% men, mean age 68 years, SD 4)<br>**Number randomised to control group:** 33 (66% men, mean age 66 years, SD 9)<br><br>**Total number included in the final analysis:** 66<br><br>**Number included in treatment group for final analysis:** 33 (36% men, mean age 68 years, SD 4)<br><br>**Number included in control group for final analysis:** 33 (66% men, mean age 66 years, SD 9) |
| Interventions | **Treatment:** citalopram (SSRI), 10 mg in participants > 66 years, 20 mg in participants < 67 years, daily; dose doubled if no response to treatment within 3 weeks<br>**Control:** matched placebo<br>**Duration:** 6 weeks; treatment continued only for responders at 6 weeks (these data not included in review)<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes** |


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**Andersen 1994** *(Continued)*

- Depression measured using the HDRS
- Proportion no longer meeting entry criteria (HDRS score < 13)
- Depression measured using the Melancholia Scale

**Secondary outcomes**

- Disability measured using the BI
- Social functioning measured using the Social Activities Index
- Cognitive functioning measured using the MMSE

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Quote:** "to ensure approximately equal numbers of patients in the treatment groups, randomization was carried out in groups of 4, with 2 assigned to citalopram"<br><br>**Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | High risk | **Comment:** opaque envelopes with codes concealed until end of the study were used. After study authors were contacted for more information, this detail was provided |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "the trial was designed as a randomized, double-blind, placebo-controlled study" (p. 1100)<br><br>**Comment:** who was blinded was not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "the trial was designed as a randomized, double-blind, placebo-controlled study" (p. 1100)<br><br>**Comment:** who was blinded was not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis (all participants including dropout were included). See Table 2 (p. 1101) for last observation for dropout carried forward |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** there were no differences in baseline demographic characteristics between groups |

**Cao 2009a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** fluoxetine (SSRI) + psychotherapy + usual care<br><br>**Control arm:** fluoxetine (SSRI) + usual care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient |


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**Cao 2009a** *(Continued)*

| | |
|---|---|
| | **Stroke criteria:** cerebral haemorrhage and infarct<br><br>**Method of stroke diagnosis:** not reported<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) 24-item HDRS score > 20; (2) can sign informed consent; (3) voluntary participation; (4) strong desire to change themselves; (5) willingness to communicate with others; (6) completion of 12 therapy sessions (treatment arm only)<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) severe cognitive impairment; (3) verbal communication barrier; (4) severe illness (e.g. myocardial infarction)<br><br>**Depression criteria:** Chinese version of 24-item HDRS score > 20<br><br>**Total number randomised in this trial:** 144 (48% of total group men; mean age of total group 60 years, SD 9)<br><br>**Number randomised to treatment group:** 72 (as above)<br><br>**Number randomised to control group:** 72<br><br>**Total number included in the final analysis:** 144 (48% of total group men; mean age of total group 60 years, SD 9)<br><br>**Number included in treatment group for final analysis:** 72 (as above)<br><br>**Number included in control group for final analysis:** 72 (as above) |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg/d + group psychotherapy with 4 phases: an introductory session to build group security and trust<br><br>**Administered by:** each group has 1 leader and 1 assistant. 2 neurologists qualified with group psychotherapy (national counsellors, grade 2) serve as leaders, and 3 nurses with professional training serve as assistants<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** fluoxetine (SSRI) 20 mg/d<br><br>**Duration of psychotherapy:** 30 to 40 minutes, once/week for 12 weeks<br><br>**Duration of fluoxetine:** first depression 4 to 6 months, then taper and discontinue; recurrent depression: extended additional 3 to 6 months; depression episodes ≥ 3 times: more prolonged period<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using 24-item HDRS<br><br>**Secondary outcomes**<br><br>• Disability measured using BI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Cao 2009a** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** ITT; no missing data reported, but randomised participants who did not complete the 12 sessions appear to have been excluded; dropouts/cross-overs not reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline 24-item HDRS and BI. Baseline demographic information not reported |

**Cao 2009b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** psychotherapy + usual care<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br><br>**Stroke criteria:** cerebral haemorrhage and infarct<br><br>**Method of stroke diagnosis:** not reported<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) 24-item HDRS score > 20; (2) can sign informed consent; (3) voluntary participation; (4) strong desire to change themselves; (5) willingness to communicate with others; (6) completion of 12 therapy sessions (treatment arm only)<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) severe cognitive impairment; (3) verbal communication barrier; (4) severe illness (e.g. myocardial infarction)<br><br>**Depression criteria:** Chinese version of 24-item HDRS > 20<br><br>**Total number randomised in this trial:** 144 (48% of total group men; mean age of total group 60 years, SD 9)<br><br>**Number randomised to treatment group:** 72 (as above)<br><br>**Number randomised to control group:** 72 (as above) |


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**Cao 2009b** *(Continued)*

| | |
|---|---|
| | **Total number included in the final analysis:** 144 (48% of total group men; mean age of total group 60 years, SD 9)<br><br>**Number included in treatment group for final analysis:** 72 (as above)<br><br>**Number included in control group for final analysis:** 72 (as above) |
| Interventions | **Treatment:** group psychotherapy with 4 phases: an introductory session to build group security and trust<br><br>**Administered by:** each group has 1 leader and 1 assistant. 2 neurologists qualified with group psychotherapy (national counsellors, grade 2) serve as leaders, and 3 nurses with professional training serve as assistants<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** usual care<br><br>**Duration of psychotherapy:** 30 to 40 minutes, once/week for 12 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using 24-item HDRS<br><br>**Secondary outcomes**<br><br>• Disability measured using BI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** ITT; no missing data reported but randomised participants who did not complete the 12 sessions appear to have been excluded; dropouts/cross-overs not reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record to compare with the publication |


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**Cao 2009b** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | **Comment:** no differences in baseline 24-item HDRS and BI; baseline demographic information not reported |

**Chen 2005a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** rTMS + cerebrovascular disease routine care<br><br>**Control arm:** cerebrovascular disease routine care |
| Participants | **Geographical location:** China<br>**Setting:** mixed outpatient and inpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995; confirmation by brain CT or MRI<br><br>**Time since stroke:** 2 months<br><br>**Inclusion criteria:** (1) disease course of stroke on average > 2 months; (2) patients and family gave informed consent<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) obvious comprehension impairment; (3) obvious aphasia; (4) severe physical illness; (5) epilepsy<br><br>**Depression criteria:** depression was diagnosed by clinical interview according to the CCMD-2-R; 17-item HDRS score > 17<br><br>**Total number randomised in this trial:** 32<br><br>**Number randomised to treatment group:** 16 (62% men, mean age 61 years, SD 4.9; modified SSS 18.3, SD 4.8)<br><br>**Number randomised to control group:** 16 (56% men, mean age 61.2 years, SD 4.7; modified SSS 17.5, SD 4.4)<br><br>**Total number included in final analysis:** 32<br><br>**Number included in treatment group for final analysis:** 16 (62% men, mean age 61 years, SD 4.9; modified SSS 18.3, SD 4.8)<br><br>**Number included in control group for final analysis:** 16 (56% men, mean age 61.2 years, SD 4.7; modified SSS 17.5 SD, 4.4) |
| Interventions | **Treatment:** low-frequency rTMS, fixed-dose 0.72 Tesla (60% of maximal stimulation intensity), frequency 0.5 Hz, 1 sequence included 30 stimulations in each side of the pre-frontal lobe; plus cerebrovascular disease routine care<br><br>**Control:** cerebrovascular disease routine care<br><br>**Treatment duration:** 1 sequence a day for 7 successive days<br><br>**Administration:** unclear<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes** |


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**Chen 2005a** *(Continued)*

- Depression measured using 17-item HDRS
- Impairments measured using modified SSS

**Secondary outcomes**

- Adverse events

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | **Comment:** randomisation performed by drawing lots, which is prone to bias |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** participants and personnel not blinded to group allocation. Study used a prospective, randomised open-blinded endpoint (PROBE) design |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** outcome assessors blinded to group allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Cullen 2018**

| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Treatment arm:** brief positive psychotherapy + usual care<br>**Control arm:** usual care |
|---|---|
| Participants | **Geographical location:** Scotland<br>**Setting:** outpatient<br>**Stroke criteria:** cerebrovascular infarct and haemorrhagic stroke<br>**Method of stroke diagnosis:** confirmed by local clinician based on clinical and/or radiological evidence<br>**Time since stroke:** 3 to 36 months |


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**Cullen 2018** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria:** (1) adults aged 18 or over; (2) diagnosis of acquired, non-progressive brain injury; (3) between 3 and 12 months post injury at time of recruitment; (4) presence of emotional distress (score in moderate or above range on at least 1 subscale of the DASS-21; (5) medically stable; (6) able to consent<br><br>**Exclusion criteria:** (1) significant communication impairment; (2) diagnosis of mild traumatic brain injury; (3) comorbid developmental learning disability or degenerative neurological condition<br><br>**Depression criteria:** presence of emotional distress (score in moderate or above range on at least 1 subscale of the DASS-21)<br><br>**Total number randomised in this trial (stroke participants only):** 24<br><br>**Number included in treatment group:** 12 (67% men; mean age 55 years, SD 10)<br><br>**Number included in control group:** 12 (67% men; mean age 60 years, SD 9)<br><br>**Total number included in final analysis** (stroke participants only)*:* 24<br><br>**Number included in treatment group for final analysis:** 12 (67% men; mean age 55 years, SD 10)<br><br>**Number included in control group for final analysis:** 12 (67% men; mean age 60 years, SD 9) |
| Interventions | **Treatment:** participants in intervention arm received a brief positive psychotherapy intervention delivered over 8 weeks, in addition to accessing usual care within the clinical service. Study intervention followed a manualised programme designed by the research team and based on aspects of Rashid and Seligman's (2013) programme, incorporating psychoeducation about ABI and positive psychology (week 1), a range of therapeutic exercises, and homework focused on using signature character strengths and reflecting on positive events (weeks 2 to 7 inclusive, with mid-point review at week 4), and final review and plan for maintenance (week 8)<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** participants in control arm received usual care within the clinical service; the content of usual care was not standardised: input varied between services and participants, but all participants could access clinical psychology input if required<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** 20 weeks |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using DASS-21 Depression<br>• Anxiety measured using DASS-21 Anxiety<br>• Stress measured using DASS-21 Stress<br>• Depression measured using AHI<br><br>**Secondary outcomes**<br><br>• Overall function measured using Mayo-Portland Adaptability Inventory-4 (MPAI-4) total (participant)<br>• Overall function measured using MPAI-4 total (informant)<br>• Caregiver Strain measured using Modified-Caregiver Strain Index |
| Notes | **Author contact:** emailed study authors to request mean, SD for DASS-21 Depression and AHI post treatment/end of follow-up. (Received reply from study author with mean SD for DASS-21 Depression, AHI, and DASS-21 Anxiety for stroke patients only 09/11/2018) |


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**Cullen 2018** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "stratified randomisation with blocking was used to allocate participants to two groups of equal size, stratified by service setting (stroke versus CTCBI). Because service setting was a proxy for injury type (stroke versus non-stroke) and for the nature of usual care that would be available to participants, either of which could have influenced outcomes, including this as a stratification factor ensured these aspects would be balanced across the intervention and control groups" (p. 24)<br><br>**Comment:** computer-generated numbers were used based on correspondence with author |
| Allocation concealment (selection bias) | Low risk | **Quote:** "the allocation system was managed by the Robertson Centre for Biostatistics and was accessed via an automated telephone service after the baseline assessment had been completed" (p. 24) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Quote:** "screening, baseline assessments, allocation and interventions were carried out by one RA (who was blinded to randomisation block length), and the interim and follow-up measures were administered by a second RA, each of whom was blind to the other's findings. The second RA was blind to participant allocation; a standard script was used to prevent unblinding during follow-up telephone calls, and postal materials included clear instructions to participants not to reveal treatment allocation information" (p. 24)<br><br>**Comment:** due to the nature of the intervention, it is unlikely that participants were blinded to the group allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "a blinded assessor administered the DASS-21 and the AHI at 5, 9 and 20 weeks post-baseline. Of 27 participants randomised (median age 57; 63% men; 82% ischaemic stroke survivors; median 5.7 months post-injury), 14 were assigned to positive psychotherapy, of whom 8 completed treatment" (p. 31) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 11/27 participants not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Du 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** rTMS + fluoxetine (SSRI)<br><br>**Control arm:** fluoxetine (SSRI) |
| Participants | **Geographical location:** China<br>**Setting:** inpatient |


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**Du 2005** *(Continued)*

| | |
|---|---|
| | **Stroke criteria:** stroke, types not stated<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995; confirmation by brain CT or MRI<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) 17-item HDRS score ≥ 8 points; (2) can sign informed consent<br><br>**Exclusion criteria:** (1) previous depression or psychiatric illness history; (2) aphasia; (3) severe cardiac, pulmonary, hepatic, and renal impairment<br><br>**Total number randomised in this trial:** 60<br><br>**Number randomised to treatment group:** 30 (53% men; age range 59 to 82 years)<br><br>**Number randomised to control group:** 30 (53% men; age range 56 to 83 years)<br><br>**Total number included in final analysis:** 60<br><br>**Number included in treatment group for final analysis:** 30<br><br>**Number included in control group for final analysis:** 30 |
| Interventions | **Treatment:** low-frequency rTMS + 20 mg fluoxetine (SSRI) daily. Patients' bilateral frontal lobes were stimulated with 60% of maximal stimulus intensity, 30 times for each side. Frequency was 0.5 Hz, 1 sequence every day continuous for 5 days as a course, with an interval of 2 days between courses<br><br>**Control:** 20 mg fluoxetine (SSRI) daily<br><br>**Treatment duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using 17-item HDRS<br>• Cognitive functioning measured using MMSE<br>• Disability measured using BI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | **Comment:** drawing lots used to generate randomisation sequence; this method of sequence generation is prone to bias |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** participants and personnel not blinded to group allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Comment:** outcome assessors not blinded to group allocation |


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**Du 2005** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | **Comment:** ITT; no missing data reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Fan 2014**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS + duloxetine (SNRI) + stroke usual care<br>**Control arm:** duloxetine (SNRI) + stroke usual care |
| Participants | **Geographical location:** China<br>**Setting:** unclear<br>**Stroke criteria:** not reported<br>**Method of stroke diagnosis:** not reported<br>**Time since stroke:** not reported<br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-2-R for depression; (2) 17-item HDRS score ≥ 8; (3) stable condition; (4) could tolerate rTMS; (5) patient or family member can sign informed consent; (6) age 18 to 80 years<br>**Exclusion criteria:** (1) with previous depression, psychiatric illness history; (2) without 1-week washout period of previous antidepressants; (3) consciousness disturbance or severe cognitive impairment; (4) with epilepsy or severe cardiac, pulmonary, hepatic, or renal disease; (5) critical conditions or unstable acute stage of stroke<br>**Depression criteria:** must meet diagnostic criteria of the CCMD-2-R for depression and the 17-item HDRS score ≥ 8<br>**Total number randomised in this trial:** 90<br>**Number randomised to treatment group:** 45 (42% men, mean age 61.43, SD 8.74)<br>**Number randomised to control group:** 45 (51% men, mean age 64.78, SD 7.23)<br>**Total number included in final analysis:** 90<br>**Number included in treatment group for final analysis:** 45 (42% men, mean age 61.43, SD 8.74)<br>**Number included in treatment group for final analysis:** 45 (51% men, mean age 64.78, SD 7.23) |
| Interventions | **Treatment:** rTMS (frequency: 1 Hz, intensity: 100% motor threshold, 30 times for a series, 10 series for each treatment; location: bilateral dorsolateral pre-frontal) + duloxetine (SNRI) 60 mg/d + stroke usual care (routine medication and rehabilitation)<br>**Control:** duloxetine (SNRI) + stroke usual care<br>**Duration:** 4 weeks |


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**Fan 2014** *(Continued)*

| | |
|---|---|
| | **Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression measured using 17-item HDRS<br>• Disability measured using MBI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** double-blind stated but who was blinded not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** double-blind stated but who was blinded not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis; no missing data reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Fang 2017**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** constructive integrative psychosocial intervention (CIPI)<br>**Control arm:** standard care |
| Participants | **Geographical location:** Singapore<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br>**Method of stroke diagnosis:** clinically diagnosed new stroke<br>**Time since stroke:** 1 week |


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**Fang 2017** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria:** (1) had satisfactory mental status MMSE > 23; (2) had clinically diagnosed new stroke within a week; (3) only patients who spoke English or Mandarin<br><br>**Exclusion criteria:** (1) other non-stroke-related neurological conditions such as brain tumour or traumatic brain injury; (2) patients discharged to a nursing home<br><br>**Depression criteria:** HADS score ≥ 8<br><br>**Total number randomised in this trial:** 42<br><br>**Number randomised to treatment group:** 23 (% men, age not recorded in the study)<br><br>**Number randomised to control group:** 19 (% men, age not recorded in the study)<br><br>**Total number included in final analysis:** 19<br><br>**Number included in treatment group for final analysis:** 13 (% men, age not recorded in the study)<br><br>**Number included in control group for final analysis:** 6 (% men, age not recorded in the study) |
| Interventions | **Treatment:** CIPI result in a positive construction of experience of illness by patients and significant others. This addresses their cognitions related to living with stroke and related behavioural response to the stroke experience. Key qualities include evidence-supported components of psychosocial-behavioural intervention life review and education<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** standard care<br><br>**Duration:** 6 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcome**<br><br>• Depression measured using HADS at 1, 3, and 6 months<br><br>**Secondary outcome**<br><br>• Cognitive functioning measured using MMSE at 1, 3, and 6 months |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "it used a randomized control group in an acute stroke unit with pretest–posttest…."<br><br>**Comment:** based on study authors' responses; random number tables used |
| Allocation concealment (selection bias) | High risk | **Comment:** based on study authors' responses; sealed envelopes used to conceal allocation. This method of allocation concealment can be tampered with |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** due to the nature of the trial, it was not possible to mask participants, clinicians, and researchers to treatment allocation |


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**Fang 2017** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | **Comment:** based on study authors' responses: outcome assessors blinded |
| Incomplete outcome data (attrition bias) All outcomes | High risk | **Comment:** per protocol analysis reported; 3/23 in treatment group not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information not reported |

**Fruehwald 2003**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Treatment arm:** fluoxetine (SSRI)<br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Austria<br>**Setting:** inpatients<br>**Stroke criteria:** ischaemic stroke and primary intracerebral haemorrhage<br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br>**Time since stroke:** 11 days<br>**Inclusion criteria:** (1) stroke on average 11 days before randomisation<br>**Exclusion criteria:** (1) MMSE < 20, more than mild communication deficit; (2) disease of the CNS and previous degenerative or expansive neurological disorder<br>**Depression criteria:** psychiatric interview and HDRS score > 15<br>**Total number randomised in this trial:** 54<br>**Number randomised to treatment group:** 28 (46% men, mean age 65 years, SD 14)<br>**Number randomised to control group:** 26 (71% men, mean age 64 years, SD 14)<br>**Total number included in final analysis:** 40<br>**Number included in treatment group for final analysis:** 22 (% men and mean age not reported)<br>**Number included in control group for final analysis:** 18 (% men and mean age not reported) |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg daily; dose escalation at 4 weeks if HDRS score > 13<br>**Control:** matched placebo<br>**Duration:** 12 weeks. Open-label treatment was continued for a further 15 months for all (these data not included in the review)<br>**Follow-up:** 18 months |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS, BDI, and CGI Scale-1<br>• Proportion of responders (HDRS < 13) |


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**Fruehwald 2003** *(Continued)*

**Secondary outcomes**

- Stroke impairment measured using SSS
- Adverse events

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "the randomization code list was generated by a computer program in a random permuted block design for each centre" (p. 348) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "all patients were randomly assigned to either fluoxetine or placebo treatment by the drug company independently of the research teams and the study centres" (p. 348) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "… neither patients nor relatives, clinical examiners nor nursing staff were aware of the drug treatment being given" (p. 348) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "… neither patients nor relatives, clinical examiners nor nursing staff were aware of the drug treatment being given" (p. 348) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 4/54 (7.4%) not included in analyses |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported. No trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** non-significant trends towards more women and right-sided lesion strokes in treatment group |

**Gao 2017a**

Methods

**Study design:** parallel design

**Number of arms:** 2

**Treatment arm:** citalopram (SSRI) + 'attention control' psychological intervention (group B)

**Control arm:** placebo + 'attention control' psychological intervention (group A)

Participants

**Geographical location:** China

**Setting:** outpatient

**Stroke criteria:** ischaemic stroke

**Method of stroke diagnosis:** occurrence of an ischaemic stroke that met the standards of WHO diagnostic criteria. Radiological MRI confirmation of an anatomical infarct observed on diffusion-weighted acute MRI

**Time since stroke:** not reported


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**Gao 2017a** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria:** (1) first-ever acute ischaemic stroke; (2) no history of depression; (3) no antidepressant treatments received before our interventions; (4) over 18 years of age<br><br>**Exclusion criteria:** (1) presence of pre-stroke disease leading to pre-stroke disability; Barthel Index < 10<br><br>**Depression criteria:** 20-item BDI scores > 10<br><br>**Total number randomised in this trial:** 136<br><br>**Number randomised to treatment group:** 91 (50% men, mean age 66 years, SD 7)<br><br>**Number randomised to control group:** 45** (53% men, mean age 67 years, SD 10)<br><br>**Total number included in final analysis:** 128<br><br>**Number included in treatment group for final analysis:** 85 (% men and mean age were not reported)<br><br>**Number included in control group for final analysis:** 43** (% men and mean age were not reported) |
| Interventions | **Treatment:** patients received active citalopram tablets (SSRI) and participated in similar placebo psychological discussions as group A<br><br>**Control:** patients received placebo tablets and participated in a placebo psychological intervention, 1-hour discussions with non-psychological clinical doctors twice a week for 3 months; discussions focused on inquiries about stroke recovery and changes in daily life<br><br>**Administered by:** non-psychological clinical doctors<br><br>**Supervision:** not reported<br><br>**Duration:** 3 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Depression measured using Melancholia Scale<br><br>**Secondary outcomes**<br><br>• Disability measured using BI |
| Notes | **Author contact:** emailed study authors to request AE tables with numbers for all groups 23 Octoer 2018 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "randomization into one of three intervention groups was undertaken by an independent researcher using computer-generated random number sequences" (p. 73) |
| Allocation concealment (selection bias) | High risk | **Quote:** "... were prepared in advance and placed in consecutively numbered, sealed, opaque envelopes" (p. 73)<br><br>**Comment:** sealed, opaque envelopes can be tampered with |
| Blinding of participants and personnel (performance bias) | High risk | **Quote:** "when patients were enrolled, they were told to participate in drug therapy, talk with doctors, and engage in rehabilitation at the same time. No breaches in blinding were detected during the trial" (p. 74) |


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**Gao 2017a** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | "the study therapists were asked not to divulge any treatment information to their patients" (p. 75)<br><br>**Comment:** therapists delivering the intervention were not blinded to group allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Quote:** "the study therapists acted as clinical evaluators…" (p. 74) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 5/91 in control, 6/91 in treatment not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Gao 2017b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** 'active' psychological intervention + placebo (group C)<br><br>**Control arm:** 'attention control' psychological intervention + placebo (group A) |
| Participants | **Geographical location:** China<br><br>**Setting:** outpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** occurrence of an ischaemic stroke that met the standards of WHO diagnostic criteria. Radiological MRI confirmation of an anatomical infarct observed on diffusion-weighted acute MRI<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) first-ever acute ischaemic stroke; (2) no history of depression; (3) no antidepressant treatments received before our interventions; (4) over 18 years of age<br><br>**Exclusion criteria:** (1) presence of pre-stroke disease leading to pre-stroke disability; Barthel Index < 10<br><br>**Depression criteria:** 20-item BDI scores > 10<br><br>**Total number randomised in this trial:** 138<br><br>**Number randomised to treatment group:** 92 (52% men, mean age 65 years, SD 8)<br><br>**Number randomised to control group:** 46** (53% men, mean age years 67, SD 10)<br><br>**Total number included in final analysis:** 130<br><br>**Number included in treatment group for final analysis:** 87 (% men and mean age not reported)<br><br>**Number included in control group for final analysis:** 43** (% men and mean age not reported) |


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**Gao 2017b** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** patients received placebo tablets and had an 'active' psychological intervention: professional cognitive-behavioural therapy with psychologists who were trained by a professional cognitive therapist for 1 week. The manual-based treatment included cognitive and behavioural courses that consisted of education, activities, graded task assignments, and identifying and modifying useless beliefs and thoughts. Interventional measures were altered to meet individual demands<br><br>**Administered by:** psychologist trained in professional cognitive therapy<br><br>**Supervision:** not reported<br><br>**Control:** patients received placebo tablets and participated in a placebo psychological intervention, 1-hour discussions with non-psychological clinical doctors twice a week for 3 months; discussions focused on inquiries about stroke recovery and changes in daily life<br><br>**Administered by:** non-psychological clinical doctors<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Duration:** 3 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Depression measured using Melancholia Scale<br><br>**Secondary outcomes**<br><br>• Disability measured using BI |
| Notes | **Author contact:** emailed study authors to request AE tables with numbers for all groups 23 October 2018 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "randomization into one of three intervention groups was undertaken by an independent researcher using computer-generated random number sequences" (p. 73) |
| Allocation concealment (selection bias) | High risk | **Quote:** "….were prepared in advance and placed in consecutively numbered, sealed, opaque envelopes" (p. 73)<br><br>**Comment:** sealed, opaque envelopes can be tampered with |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "when patients were enrolled, they were told to participate in drug therapy, talk with doctors, and engage in rehabilitation at the same time. No breaches in blinding were detected during the trial" (p. 74)<br><br>"the study therapists were asked not to divulge any treatment information to their patients" (p. 75)<br><br>**Comment:** therapists delivering the intervention not blinded to group allocation |
| Blinding of outcome assessment (detection bias) | High risk | **Quote:** "the study therapists acted as clinical evaluators …" (p. 74) |


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**Gao 2017b** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | High risk | **Comment:** per protocol analysis reported only; 5/91 in control, 6/91 in treatment not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Gu 2016**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Treatment arm:** rTMS<br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** South Korea<br>**Setting:** unclear<br>**Number of participants:** 24<br>**Stroke criteria:** infarct and haemorrhage<br>**Method of stroke diagnosis:** not reported<br>**Time since stroke:** > 6 months<br>**Inclusion criteria:** (1) absence of depression or medication history of antidepressants before stroke onset; (2) absence of severe cognitive dysfunction or aphasia; (3) absence of serious medical complications such as pneumonia or cardiac problems; (4) admitted > 6 months after stroke onset; (5) aged between 21 and 80 years only<br>**Exclusion criteria:** (1) history of depression before stroke onset; (2) medication history of antidepressants before stroke onset; (3) serious medical complications such as pneumonia or cardiac problems<br>**Depression criteria:** BDI scores > 12 and 17-item HDRS scores > 6<br>**Total number randomised in this trial:** 24<br>**Number randomised to treatment group:** 12 (50% men, mean age 58 years, SD 9)<br>**Number randomised to control group:** 12 (42% men, mean age 58 years, SD 8)<br>**Total number included in final analysis:** 24<br>**Number included in treatment group for final analysis:** 12 (50% men, mean age 58 years, SD 9)<br>**Number included in control group for final analysis:** 12 (42% men, mean age 58 years, SD 8) |
| Interventions | **Treatment:** Magstim Super Rapid Magnetic Stimulator (The Magstim Company, Wales, UK) with 70-mm, air-cooled coil in the shape of a figure of 8. The coil was held with the handle posterior and oriented sagittally. rTMS was performed over the left F3 on the scalp according to the 10/20 electroencephalography system (i.e. the DLPFC). For patients in the rTMS group, rTMS was delivered over the DLPFC at 10 Hz, at an intensity of 110% of the motor threshold, duration of 5 seconds, and total of 20 |


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**Gu 2016** *(Continued)*

| | |
|---|---|
| | trains separated by 1-minute pauses (total of 1000 pulses). Each patient underwent 10 consecutive sessions (Monday to Friday, 5 times per week for 2 weeks)<br><br>**Control:** sham stimulation was delivered using the same protocol, except that the angle of the coil was at 90 perpendicular to the skull rather than tangential to it. Thus, the magnetic field could not penetrate the brain, although patients could hear the sound that was produced<br><br>**Administered by:** psychiatrist<br><br>**Duration:** 2 weeks<br><br>**Follow-up:** 4 weeks |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using BDI and 17-item HDRS<br><br>**Secondary outcomes**<br><br>• Motor function measured using Upper limb Motoricity Index (MI-UE), lower limb MI-LE, Modified Brunnstrom Classification (MBC), and Functional Ambulatory Category (FAC) |
| Notes | **Author contact:** emailed study authors for method of randomisation, details of blinding of patients, method of stroke diagnosis, number of patients screened/eligible, and sample size calculations 24 October 2018 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Quote:** "all patients were randomly assigned to two groups, the rTMS and sham groups**…**"**(**p. 271)<br><br>**Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Quote:** "a psychiatrist who was blinded to the study protocol performed rTMS using a Magstim Super Rapid Magnetic Stimulator" (p. 271)<br><br>**Comment:** double-blind stated but not reported whether participants were blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "the experimenters who applied the rTMS or sham stimulations were different from the experimenters who assessed the degree of depression and motor function. The experimenters who assessed depression and motor function were blinded to the group assignment" (p. 271) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; all participants included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol or registry record available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline BDI scores and demographic characteristics between groups |


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**Hoffmann 2015**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** cognitive-behavioural therapy<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** Australia<br>**Setting:** inpatient<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** diagnosis of stroke confirmed by chart review<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) > 18 years old; (2) adequate cognitive capacity to provide informed consent; (3) adequate English and expressive and receptive communication skills<br><br>**Exclusion criteria:** (1) neurodegenerative disorder (e.g. dementia); (2) living > 50 km away from hospital<br><br>**Depression criteria:** depression score not an entry criteria. For unpublished analysis, HADS ≥ 8 used for depression criteria<br><br>**Total number randomised in this trial:** 22<br><br>**Number randomised to treatment group:** 12 (75% men; mean age 60.8, SD 11.7)<br><br>**Number randomised to control group:** 10 (60% men; mean age 57.0, SD 14.2)<br><br>**Total number included in final analysis:** 17<br><br>**Number included in treatment group for final analysis:** 12 (75% men; mean age 60.8, SD 11.7)<br><br>**Number included in control group for final analysis:** 5 (60% men; mean age 57.0, SD 14.2) |
| Interventions | **Treatment:** 8 × 1-hour cognitive-behavioural coping skills sessions delivered by clinical psychologist with first 2 sessions in hospital, then 6 delivered at home<br><br>**Administered by:** clinical psychologist<br><br>**Supervision:** psychologist<br><br>**Intervention fidelity:** 9/11 patients received 8 sessions; 7/11 received sessions in the intended location<br><br>**Control:** usual care<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** 3 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HADS and MADRS<br>• Anxiety measured using HADS<br><br>**Secondary outcomes**<br><br>• Disability measured using MBI<br>• Self-efficacy measured using Stroke Self Efficacy Questionnaire |


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**Hoffmann 2015** *(Continued)*

- Functional capacity measured using Nottingham EADL
- Knowledge of stroke measured using Stroke Knowledge Questionnaire
- Quality of life measured using SAQoL

| | |
|---|---|
| Notes | This trial had 3 arms (self-management therapy, cognitive-behavioural therapy, and usual care), but only data from cognitive-behavioural therapy compared with usual care (n = 17 participants) are presented here |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "... randomly allocated using a predetermined computer generated randomisation sequence ..." (p. 118) |
| Allocation concealment (selection bias) | High risk | **Comment:** sealed opaque envelopes reported; this method of allocation concealment can be tampered with |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** due to the nature of the trial, it was not possible to mask participants, personnel delivering the intervention, and researchers to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "outcomes were assessed in a face-to-face interview conducted by a research assistant (a registered psychologist) who was blind to group allocation" (p. 118) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Quote:** "analysis was completed using ... and on an intention to treat basis and missing data were addressed using the last observation carried forward procedure" (p. 120)<br><br>**Comment:** ITT analysis reported. From whole data set, including depressed and non-depressed, 1 intervention and 1 control withdrew post randomisation |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information not reported |

**Huang 2002**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** fluoxetine (SSRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br><br>**Stroke criteria:** first-ever ischaemic or haemorrhagic stroke<br><br>**Method of stroke diagnosis:** diagnosis is consistent with the diagnostic criteria for acute stroke formulated by the Chinese Medical Association with 1 single and unilateral lesion confirmed by brain CT or MRI |


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**Huang 2002** *(Continued)*

| | |
|---|---|
| | **Time since stroke:** unclear<br><br>**Inclusion criteria:** none reported<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) severe heart disease; (3) previous organic brain disease; (4) severe liver or kidney disease; (5) history of drug allergy<br><br>**Depression criteria:** psychiatric interview to confirm diagnosis meets depression diagnostic criteria of the CCMD-2-R<br><br>**Total number randomised in this trial:** 80 (overall percentage of men 45%; 80 patients were a depressive subgroup of 168 patients whose mean age was 62.2 years, SD 8.1)<br><br>**Number randomised to treatment group:** 40 (% men and mean age in treatment group not reported)<br><br>**Number randomised to control group:** 40 (% men and mean age in control group not reported; total group as above)<br><br>**Total number included in final analysis:** 80 (overall percentage of men 45%; 80 patients were a depressive subgroup of 168 patients whose mean age was 62.2 years, SD 8.1)<br><br>**Number included in treatment group for final analysis:** 40 (% men and mean age in treatment group not reported)<br><br>**Number included in control group for final analysis:** 40 (% men and mean age in control group not reported; total group as above) |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg/d in the morning<br><br>**Control:** matched placebo<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using CCMD-2-R and 17-item HDRS<br><br>**Secondary outcomes**<br><br>• Neurological impairment measured using CSS<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias) | Unclear risk | **Comment:** blinding of outcome assessors not reported |


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**Huang 2002** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline HAMD and CSS scores between groups |

**Jiang 2001a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** amitriptyline (TCA)<br><br>**Control arm:** placebo (not matched) |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** diagnosis via CT or MRI (100%)<br><br>**Time since stroke:** 0 to 7 days<br><br>**Inclusion criteria:** (1) Chinese Stroke Scale score > 8; (2) can independently complete HDRS, aged < 80 years; (3) no severe negative life events in past year; (4) first stroke; (5) no previous psychosis; (6) no antidepressant medication<br><br>**Exclusion criteria:** (1) with history of psychosis; (2) on antidepressant medication<br><br>**Depression criteria:** HDRS > 8<br><br>**Total number randomised in this trial:** 45<br><br>**Number randomised to treatment group:** 30 (57% men, mean age 62 years, SD 14)<br>**Number randomised to control group:** 15** (60% men, mean age 63 years, SD 15)<br><br>**Total number included in final analysis:** 45<br><br>**Number included in treatment group for final analysis:** 30 (57% men, mean age 62 years, SD 14)<br><br>**Number included in control group for final analysis:** 15** (60% men, mean age 63 years, SD 15) |
| Interventions | **Treatment:** amitriptyline (TCA) 50 mg increasing by 25 mg per day to 200 mg daily<br>**Control:** placebo (not matched) 2 tablets per day<br>**Duration:** 6 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Impairment measured using CSS |


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**Jiang 2001a** *(Continued)*

- Adverse events

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | High risk | **Comment:** 3-armed trial. Placebo frequency matched to Deanxit (intervention in third arm) - not to amitriptyline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** participants blinded but personnel not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported (complete follow-up of all randomised participants) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | High risk | **Comment:** intervention group was younger and had higher HDRS score and lower CSS score |

**Jiang 2001b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** Deanxit<br><br>**Control arm:** placebo (not matched) |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** diagnosis via CT or MRI (100%)<br><br>**Time since stroke:** 0 to 7 days<br><br>**Inclusion criteria:** (1) CSS score > 8; (2) can independently complete HDRS, aged < 80 years; (3) no severe negative life events in past year; (4) first stroke; (5) no previous psychosis; (6) no antidepressant medication<br><br>**Exclusion criteria:** (1) with history of psychosis; (2) on antidepressant medication<br><br>**Depression criteria:** HDRS > 8 |


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**Jiang 2001b** *(Continued)*

| | |
|---|---|
| | **Total number randomised in this trial:** 45<br><br>**Number randomised to treatment group:** 30 (58% men, mean age 62 years, SD 14)<br><br>**Number randomised to control group:** 15** (60% men, mean age 63 years, SD 15)<br><br>**Total number included in final analysis:** 45<br><br>**Number included in treatment group for final analysis:** 30 (58% men, mean age 62 years, SD 14)<br><br>**Number included in control group for final analysis:** 15** (60% men, mean age 63 years, SD 15) |
| Interventions | **Treatment:** Deanxit 2 tablets daily<br>**Control:** placebo (not matched but frequency matched)<br>**Duration:** 6 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Impairment measured using CSS<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | High risk | **Comment:** 3-armed trial. Placebo frequency matched to Deanxit (intervention in third arm) - not to amitriptyline |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** participants blinded but personnel not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported (complete follow-up of all randomised participants) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | High risk | **Comment:** intervention group was younger and had higher HDRS score and lower CSS score |


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**Jiang 2014a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** TMS + acute stroke usual care<br><br>**Control arm:** acute stroke usual care |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** Internal carotid artery territory infarct<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Time since stroke:** 3 to 10 days<br><br>**Inclusion criteria:** (1) first-ever stroke; (2) age 30 to 70 years; (3) NIHSS at admission 8 to 20 points; (4) GCS scale score > 8; (5) education level: at least high school, able to complete questionnaires; (6) no communication barriers, able to communicate with medical staff; (7) can sign informed consent<br><br>**Exclusion criteria:** (1) comorbid severe organ failure; (2) history of epilepsy or consciousness disturbance; (3) contraindication for transcranial magnetic stimulation such as pacemaker implanted, severe cardiac dysrhythmia; (4) worsened clinical condition, new infarct, or haemorrhagic transformation<br><br>**Depression criteria:** not reported<br><br>**Total number randomised in this trial:** 100<br><br>**Number randomised to treatment group:** 50 (% men and mean age not reported)<br><br>**Number randomised to control group:** 50 (% men and mean age not reported)<br><br>**Total number included in final analysis:** 100<br><br>**Number included in treatment group for final analysis:** 50 (% men and mean age not reported)<br><br>**Number included in control group for final analysis:** 50 (% men and mean age not reported) |
| Interventions | **Treatment:** TMS + acute stroke usual care; frequency: start 3 to 10 days after stroke onset, 2 times a day, 20 minutes each time, for successive 14 days; location: motor cortex on the healthy side<br><br>**Control:** acute stroke usual care<br><br>**Duration:** 12 weeks<br><br>**Follow-up:** 3 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br>• Activities of daily living measured using ADL |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Jiang 2014a** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random numbers table used for sequence generation |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** outcome assessors blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 1 participant dropped out and was not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Jiang 2014b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** TMS + sertraline (SSRI) + acute stroke usual care<br><br>**Control arm:** sertraline (SSRI) + acute stroke usual care |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** internal carotid artery territory infarct<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Time since stroke:** 3 to 10 days<br><br>**Inclusion criteria:** (1) first-ever stroke; (2) age 30 to 70 years; (3) NIHSS at admission 8 to 20 points; (4) GCS scale score > 8; (5) education level: at least high school, able to complete questionnaires; (6) no communication barriers, able to communicate with medical staff; (7) can sign informed consent<br><br>**Exclusion criteria:** (1) comorbid severe organ failure; (2) history of epilepsy or consciousness disturbance; (3) contraindication for transcranial magnetic stimulation such as pacemaker implanted, severe cardiac dysrhythmia; (4) worsening clinical condition, new infarct, or haemorrhagic transformation<br><br>**Depression criteria:** not reported<br><br>**Total number randomised in this trial:** 100<br><br>**Number randomised to treatment group:** 50 (% men and mean age not reported)<br><br>**Number randomised to control group:** 50 (% men and mean age not reported) |


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**Jiang 2014b** *(Continued)*

| | |
|---|---|
| | **Total number included in final analysis:** 99<br>**Number included in treatment group for final analysis:** 50<br>**Number included in control group for final analysis:** 49 |
| Interventions | **Treatment:** TMS + sertraline (SSRI) 50 mg/d + acute stroke usual care; frequency: start 3 to 10 days after stroke onset, 2 times a day, 20 minutes each time, for successive 14 days, location: motor cortex on the healthy side<br>**Control:** sertraline (SSRI) 50 mg/d + acute stroke usual care<br>**Duration:** 12 weeks<br>**Follow-up:** 3 months |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br>• Activities of daily living measured using ADL |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random numbers table used for sequence generation |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** outcome assessors blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 1 participant dropped out and was not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Jin 2013**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2 |


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**Jin 2013** *(Continued)*

| | |
|---|---|
| | **Experimental arm:** rTMS + sertraline (SSRI) + usual care<br><br>**Control arm:** sertraline (SSRI) + usual care |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Inclusion criteria:** (1) without cerebral haemorrhage; (2) cerebral infarct history; (3) without epilepsy history; (4) EEG showing no epileptiform discharge; (5) without head injury or intracranial infection history; (6) without intracranial metal or other foreign body<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** 17-item HDRS score ≥ 17<br><br>**Total number randomised in this trial:** 60<br><br>**Number randomised to treatment group:** 30 (63% men; mean age 56.0, SD 9.8)<br><br>**Number randomised to control group:** 30 (51% men; mean age 54.0, SD 10.2)<br><br>**Total number included in final analysis:** 60<br><br>**Number included in treatment group for final analysis:** 30<br><br>**Number included in control group for final analysis:** 30 |
| Interventions | **Treatment:** rTMS + sertraline (SSRI) 100 mg/d + usual care; frequency: 10 Hz, intensity: 80% resting motor threshold, with each stimulation lasting 4 seconds with an interval of 56 seconds, total 20 minutes each treatment, 1 treatment per day, 5 treatments per week, location: left DLPFC<br><br>**Control:** sertraline (SSRI) 100 mg/d + usual care<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using 17-item HDRS<br>• Impairment measured using NIHSS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias) | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |


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**Jin 2013** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Kerr 2018**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** individual motivational interviewing<br>**Control arm:** usual care |
| Participants | **Geographical location:** Australia<br>**Setting:** inpatient<br>**Stroke criteria:** cerebral infarction/intracerebral haemorrhage<br>**Method of stroke diagnosis:** medical diagnosis confirmed by neurologist in the medical notes<br>**Time since stroke:** not reported<br>**Inclusion criteria:** (1) acute presentation after acute stroke (cerebral infarction/intracerebral haemorrhage; (2) cognitively alert<br>**Exclusion criteria:** (1) subarachnoid haemorrhage; (2) mental health conditions, including depressive symptoms requiring professional support within 1 month; (3) severe communication problems (e.g. significant dysphasia or aphasia); (4) myocardial infarction; (5) concurrent neurological disease/trauma<br>**Depression criteria:** none<br>**Total number randomised in this trial (stroke participants only):** 10<br>**Number randomised to treatment group:** 4 (25% men, mean age 57 years, SD 20.8)<br>**Number randomised to control group:** 6 (50% men, mean age 65.8 years, SD 12.9)<br>**Total number included in final analysis (stroke participants only):** 9<br>**Number randomised to treatment group:** 4<br>**Number included in control group:** 5 |
| Interventions | **Treatment:** the over-arching principle of the intervention was to support the stroke survivor in adjusting to life after stroke. The purpose of Session 1 was to set the agenda and encourage the patient to talk about adjustment to stroke. In Session 2, the patient was encouraged to identify realistic goals for recovery and barriers to achieving goals. In Session 3, the goals were to identify any ambivalence that the patient had about achieving goals; to support the patient's optimism and self-efficacy, and to as- |


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**Kerr 2018** *(Continued)*

| | |
|---|---|
| | sist in identification of solutions to problems. Participants were encouraged to summarise their goals and commitment and to clarify any information from the first 2 sessions. Sessions were scheduled for 30 minutes<br><br>**Administered by:** trained facilitators<br><br>**Supervision:** not stated<br><br>**Intervention fidelity:** not reported<br><br>**Control:** usual care<br><br>**Duration:** not reported<br><br>**Follow-up:** 1 month and 3 months |
| Outcomes | **Primary outcomes**<br><br>• Feasibility (application, recruitment, and retention)<br><br>**Primary clinical outcomes**<br><br>• Depression measured using HADS and PHQ-9<br>• Anxiety measured using HADS<br>• Quality of life measured using quality of life Index<br><br>**Secondary outcomes**<br><br>• Disability measured using MBI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a computer-generated block randomisation list equally divided all numbers between 1 and 60 into either treatment or control groups" (p. 3) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "allocation to the intervention or control arms was concealed from participants until after recruitment and baseline data collection. Envelopes were prepared by the Principal Investigator and stored in a locked cupboard in the ward. The envelopes were numbered sequentially, indicating the order in which participants were enrolled into the study (e.g. the first participant received the envelope labelled "Number 1", the second participant received the envelope "Number 2", etc.). A note in the envelope indicated the allocation (to intervention or control group), concealed by coloured paper to protect the identity of the allocation group. The project manager opened the randomisation envelopes after baseline data collection" (p. 3) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "allocation to the intervention or control arms was concealed from participants until after recruitment and baseline data collection" (p. 3) "Although intentionally blinded, the research assistant may have become aware of the allocation in conversation with the participant" (p. 5) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Quote:** "the research assistant, a nurse with significant research experience, was employed to collect data at the 2 follow-up time points. Although intentionally blinded, the research assistant may have become aware of the allocation in conversation with the participant" (p. 5) |
| Incomplete outcome data (attrition bias) | Unclear risk | **Comment:** per protocol analysis reported only; 10/48 participants not included in the analysis |


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**Kerr 2018** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | **Comment:** Barthel Index not reported in the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Kirkness 2017a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** brief psychosocial-behavioural intervention (in-person)<br>**Control arm:** usual care |
| Participants | **Geographical location:** USA<br>**Setting:** outpatient<br>**Stroke criteria:** ischaemic or haemorrhagic stroke<br>**Method of stroke diagnosis:** ischaemic or haemorrhagic stroke (verified by CT or MRI)<br>**Time since stroke:** 4 months<br>**Inclusion criteria:** (1) those with ischaemic or haemorrhagic stroke; (2) GDS score > 11; (3) within 4 months of stroke onset<br>**Exclusion criteria:** (1) GDS score < 11; (2) not within 4 months of stroke onset<br>**Depression criteria:** GDS score < 11<br>**Total number randomised in this trial:** 49<br>**Number randomised to treatment group:** 35 (48.6% men, mean age 58.5 years, SD not reported)<br>**Number randomised to control group:** 14** (50% men, mean age 60.7 years, SD not reported)<br>**Total number included in final analysis:** 44<br>**Number included in treatment group for final analysis:** 31<br>**Number included in control group for final analysis:** 13** |
| Interventions | **Treatment:** brief in-person psychosocial-behavioural intervention (had 1 in-person orientation session with the psychosocial nurse practitioner therapist, either at home or at our study offices. Participant received participant manuals, discussed goals and expectations of each session, and learned how to fill out homework sections<br>**Administered by:** psychosocial nurse practitioner therapist<br>**Supervised by:** not reported<br>**Treatment fidelity:** not reported<br>**Control:** usual care (participants reported on their progress at follow-up visits in their homes from research nurses at 8 weeks, 21 weeks, and 12 months following entry to the study).<br>**Duration:** 8 weeks |


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**Kirkness 2017a** *(Continued)*

| | |
|---|---|
| | **Follow-up:** 10 months |
| Outcomes | **Primary outcomes**<br>• Response (per cent reduction in HDRS)<br>• Remission (HDRS score < 10) at 8 weeks and 12 months post treatment |
| Notes | Emailed study authors to request mean and SD for HDRS, BI, and NIHSS score at 8 weeks and 12 months post treatment for all 3 groups 23 October 2018 (reply received - mean SD and remission for HDRS and BI for all treatment groups sent by study author 06/11/2018) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "the algorithm was based on an imbalance score which measured, for a given set of random assignments, how far out of balance the study would be within strata for each factor and then summed over factors. When a new subject was available for randomization, we computed what the imbalance score would be if this subject were assigned to usual care, or to telephone intervention, or to in-person intervention. Then randomization was done to allocate two intervention participants to each control with each new assignment having a higher probability of less imbalance. The schema did not require equal numbers in each arm" (p. 4) |
| Allocation concealment (selection bias) | Unclear risk | **Quote:** "the study statistician generated the algorithm, which was securely stored and accessible only by the statistician and research nurse supervisor" (p. 5)<br>**Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "participants were asked not to reveal their study arm to the outcome assessors" (p. 5)<br>**Comment:** blinding of personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "... masking outcome assessors to the participant's randomization status. Participants were asked not to reveal their study arm to the outcome assessors. We did not detect any breaches in masking" (p. 5) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only. 9 participants not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Kirkness 2017b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** brief psychosocial-behavioural intervention (telephone) |


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**Kirkness 2017b** *(Continued)*

| | |
|---|---|
| | **Control arm:** usual care |
| Participants | **Geographical location:** USA<br><br>**Setting:** outpatient<br><br>**Stroke criteria:** ischaemic or haemorrhagic stroke<br><br>**Method of stroke diagnosis:** ischaemic or haemorrhagic stroke (verified by CT or MRI)<br><br>**Time since stroke:** 4 months<br><br>**Inclusion criteria:** (1) ischaemic or haemorrhagic stroke; (2) GDS score > 11; (3) within 4 months of stroke onset<br><br>**Exclusion criteria:** (1) GDS score < 11; (2) not within 4 months of stroke onset<br><br>**Depression criteria:** GDS score < 11<br><br>**Total number randomised in this trial:** 51<br><br>**Number randomised to treatment group:** 37 (51.4% men, mean age 61.7 years, SD not reported)<br><br>**Number randomised to control group:** 14** (50% men, mean age 60.7 years, SD not reported)<br><br>**Total number included in final analysis:** 47<br><br>**Number included in treatment group for final analysis:** 34<br><br>**Number included in control group for final analysis:** 13** |
| Interventions | **Treatment:** brief telephone psychosocial-behavioural intervention (had 1 in-person orientation session with psychosocial nurse practitioner therapist, either at home or at our study offices. Participants received participant manuals, discussed goals and expectations of each session, and learned how to fill out homework sections<br><br>**Administered by:** psychosocial nurse practitioner therapist<br><br>**Supervised by:** not reported<br><br>**Treatment fidelity:** not reported<br><br>**Control:** usual care (participants reported on their progress at follow-up visits in their homes from research nurses at 8 weeks, 21 weeks, and 12 months following entry to the study)<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** 10 months |
| Outcomes | **Primary outcomes**<br><br>• Response (per cent reduction in HDRS)<br>• Remission (HDRS score < 10) at 8 weeks and 12 months post treatment |
| Notes | Emailed study authors to request mean and SD for HDRS, BI, and NIHSS score at 8 weeks and 12 months post treatment for all 3 groups 23/10/2018 (reply received - mean SD and remission for HDRS and BI for all treatment groups sent by trial author 06/11/2018) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "the algorithm was based on an imbalance score which measured, for a given set of random assignments, how far out of balance the study would be |


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**Kirkness 2017b** *(Continued)*

| | | |
|---|---|---|
| | | within strata for each factor and then summed over factors. When a new subject was available for randomization, we computed what the imbalance score would be if this subject were assigned to usual care, or to telephone intervention, or to in-person intervention. Then randomization was done to allocate two intervention participants to each control with each new assignment having a higher probability of less imbalance. The schema did not require equal numbers in each arm" (p. 4) |
| Allocation concealment (selection bias) | Unclear risk | **Quote:** "the study statistician generated the algorithm, which was securely stored and accessible only by the statistician and research nurse supervisor" (p. 5)<br><br>**Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "participants were asked not to reveal their study arm to the outcome assessors" (p. 5)<br><br>**Comment:** blinding of personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "….masking outcome assessors to the participant's randomization status. Participants were asked not to reveal their study arm to the outcome assessors. We did not detect any breaches in masking" (p. 5) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 9 participants not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Kong 2007**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** fluoxetine (SSRI) 20 mg/d<br><br>**Control arm:** placebo |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** diagnosis met the diagnostic criteria of various cerebrovascular diseases formulated at the 4th National Cerebrovascular Disease Conference and confirmed as stroke by skull CT or MRI<br><br>**Time since stroke:** < 7 days<br><br>**Inclusion criteria:** (1) all patients were < 7 days from their first-ever stroke; (2) able to understand and carry out verbal instructions<br><br>**Exclusion criteria:** (1) diagnosis of major depression at evaluation or at any earlier period during the index episode; (2) active suicidal ideation; (3) bipolar disorder, schizophrenia, or other psychotic disor- |


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**Kong 2007** *(Continued)*

| | |
|---|---|
| | der; (4) currently taking antidepressants; (5) MMSE score ≤ 23; (6) medical contraindication to fluoxetine; (7) history of allergy to fluoxetine; (8) history of substance abuse; (9) obvious liver and renal function deficit<br><br>**Depression criteria:** 24-item HDRS score ≥ 8 and ≤ 20<br><br>**Total number randomised in this trial:** 90<br>**Number randomised to treatment group:** 48 (60% men; mean age 64 years, SD 7; 62% ischaemic; NIHSS 14.6, SD 5.8)<br><br>**Number randomised to control group:** 42 (58% men; mean age 62 years, SD 7; 58% ischaemic; NIHSS 14.3, SD 6.1)<br><br>**Total number included in final analysis:** 73<br><br>**Number included in treatment group for final analysis:** 37<br><br>**Number included in control group for final analysis:** 36 |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg/d; no further details given<br><br>**Control:** placebo (vitamin C). Dose not specified but capsules described as identical to treatment capsules<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using 24-item HDRS<br><br>**Secondary outcomes**<br><br>• Functional capacity measured using BI<br>• Impairment measured using NIHSS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "treatment allocation was based on a computer-generated list of treatment numbers" (p. 163) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "….were given as a single morning dose in identical capsules in coded boxes" (p. 163) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "the patient, relatives and the researchers were not aware of the drug being given" (p. 163)<br><br>**Comment:** blinding of those who delivered the intervention not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Quote:** "seventy-three of the 90 randomized patients accomplished the trial. In the treatment group, 11 patients dropped out, including insufficient clinical response (n = 4), somatic side effects (n = 2), intervening medical illness (n = 1), hypomania (n = 3), and other reasons (n = 2). In the placebo group, 6 patients |


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**Kong 2007** *(Continued)*

| | | |
|---|---|---|
| | | existed, including insufficient clinical response (n = 2), somatic side effects (n = 1) and other reasons (n = 3)"<br><br>**Comment:** per protocol analysis reported only |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Lai 2006a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** paroxetine (SSRI)<br><br>**Control arm:** placebo |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br><br>**Stroke criteria:** acute stroke<br><br>**Method of stroke diagnosis:** diagnosis via CT<br><br>**Time since stroke:** unclear<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** HDRS score > 6<br><br>**Total number randomised in this trial:** 80<br><br>**Number included in treatment group:** 40 (54% men in total, mean age 60 years, SD 14)<br>**Number included in control group:** 40 (54% men in total, mean age 60 years, SD 14)<br><br>**Total number included in final analysis:** 80<br><br>**Number included in treatment group for final analysis:** 40<br><br>**Number included in control group for final analysis:** 40 |
| Interventions | **Treatment:** paroxetine (SSRI) 20 mg/d<br>**Control:** placebo<br>**Duration:** 2 months<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS and ZDS<br>• Impairment measured using SSS<br><br>**Secondary outcomes**<br><br>• Death |


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**Lai 2006a** *(Continued)*

- Adverse events

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported (complete follow-up of all randomised participants) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information not reported |

**Li 2008**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** fluoxetine (SSRI)<br>**Control arm:** matched placebo |
| Participants | **Geographical location:** China.<br>**Setting**: unclear<br>**Stroke criteria:** ischaemic or haemorrhagic stroke<br>**Method of stroke diagnosis:** each patient evaluated for inclusion by a neuro-psychiatrist. Presence of recent < 6 weeks ischaemic or haemorrhagic stroke documented by CT or MRI before the study<br>**Time since stroke:** 4.78 days<br>**Inclusion criteria:** (1) lack of treatment with antidepressants during the 2 weeks before this study; (2) only single ischaemic and haemorrhagic stroke<br>**Exclusion criteria:** (1) cognitive impairment (MMSE < 23); (2) severe aphasia; (3) history of alcoholism, abnormal thyroid, or epilepsy<br>**Depression criteria:** HDRS score > 20 |


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**Li 2008** *(Continued)*

| | |
|---|---|
| | **Total number randomised in this trial:** 90<br><br>**Number randomised to treatment group:** 60 (47% men; mean age 68.5 years, SD 4.1; mean time since stroke 4.83 weeks, SD 0.57)<br><br>**Number randomised to control group:** 30 (57% men; mean age 67.8 years, SD 3.9; mean time since stroke 4.82, SD 0.67)<br><br>**Total number included in final analysis:** 86<br><br>**Number included in treatment group for final analysis:** 58<br><br>**Number included in control group for final analysis:** 28 |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 to 40 mg depending on tolerability together with placebo to make up 6 tablets<br><br>**Control:** matched placebo (composition not specified) 18 grams in 6 tablets twice daily<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS (mean HDRS score at end of trial)<br>• Percentage of responders (measure of clinical response defined as > 50% reduction in HDRS score compared with baseline score)<br><br>**Secondary outcomes**<br><br>• Depression measured using HDRS (at 4 weeks) |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a computer-generated randomisation was carried out…" (p. 843) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "both placebo and herbal tablets were prepared to be identical to the fluoxetine…" (p. 842) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "neither the examiners involved nor the patients were aware of the type of the administered medications" (p. 842)<br><br>**Comment:** physician initiated and moderated treatment dose based on patient's tolerability and response. It is likely that the physician was not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "neither the examiners involved nor the patients were aware of the type of the administered medications" (p. 842) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** 2/60 patients in the fluoxetine group withdrew from the study due to recurrent stroke; 2/30 withdrew due to increased depressive symptoms within 4 weeks of the start of the trial. Per protocol analysis reported only |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |


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**Li 2008** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Li 2013**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS + mirtazapine + stroke usual care<br><br>**Control arm:** mirtazapine + stroke usual care |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria**: not reported<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Inclusion criteria:** (1) aged over 65 years; (2) patient or guardian can sign informed consent; (3) meeting diagnostic criteria of the CCMD-3 for depression<br><br>**Exclusion criteria:** (1) comorbid with aphasia, comprehension, or expression impairment, or severe mental retardation; (2) with severe cardiac, hepatic, or renal disease, or with epilepsy; (3) intracranial metal implant, possible history of allergy to mirtazapine<br><br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression and 17-item HDRS score ≥ 17<br><br>**Total number randomised in this trial:** 60<br><br>**Number included in treatment group:** 30 (56% men; mean age 64.8, SD 5.4)<br><br>**Number included in control group:** 30 (53% men; mean age 65.2, SD 4.8)<br><br>**Total number included in final analysis:** 60<br><br>**Number included in treatment group for final analysis:** 30<br><br>**Number included in control group for final analysis:** 30 |
| Interventions | **Treatment:** rTMS + mirtazapine (starting from 15 mg/d at night, if tolerable, increase to 30 mg/d in 2 to 3 days) + stroke usual care (medications + rehabilitation). Frequency: 1 Hz, intensity: 90% motor threshold, each treatment lasting for 20 minutes, 5 treatments a week, location: right DLPFC<br><br>**Control:** mirtazapine + stroke usual care<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Impairment measured using NIHSS |


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**Li 2013** *(Continued)*

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no significant differences in baseline demographics between groups |

**Li 2014**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS + fluoxetine (SSRI) + stroke usual care<br>**Control arm:** fluoxetine (SSRI) + stroke usual care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) 17-item HDRS score ≥ 18<br>**Exclusion criteria:** not reported<br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression and for 17-item HDRS score ≥ 18<br>**Total number randomised in this trial:** 93 |


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**Li 2014** *(Continued)*

| | |
|---|---|
| | **Number randomised to treatment group:** 47 (49% men; mean age 57.6, SD 6.8)<br>**Number randomised to control group:** 46 (52% men; mean age 56.5, SD 6.7)<br>**Total number included in final analysis:** 93<br>**Number included in treatment group for final analysis:** 47<br>**Number included in control group for final analysis:** 46 |
| Interventions | **Treatment:** rTMS + fluoxetine (SSRI) 20 mg/d + stroke usual care (medications + rehabilitation)<br>Frequency: 10 Hz, intensity: 80% motor threshold, with each series lasting 4 seconds with an interval of 56 seconds, successive 20 series per day, 5 treatments a week, location: left DLPFC<br>**Control:** fluoxetine (SSRI) + stroke usual care<br>**Duration:** 4 weeks<br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Disability measured using MBI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random number table used for sequence generation |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |


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**Lincoln 2003**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 3<br><br>**Experimental arm:** cognitive-behavioural therapy<br><br>**Control arm 1:** attention control<br><br>**Control arm 2:** usual care |
| Participants | **Geographical location:** UK<br>**Setting:** outpatient<br><br>**Stroke criteria:** all subtypes<br><br>**Method of stroke diagnosis:** diagnosis via clinical signs and symptoms and CT<br><br>**Time since stroke:** 1 to 6 months<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) blindness; (2) deafness; (3) participant did not speak English; (4) dementia documented in medical records; (5) treated for depression in previous 5 years; (6) lived outside specified locality; (7) participant could not complete questionnaire unaided<br><br>**Depression criteria:** psychiatric interview (SCAN), BDI score > 10, WDI score > 18<br><br>**Total number randomised in this trial:** 123<br><br>**Number randomised to treatment group:** 39 (51% men, mean age 67 years, SD 13)<br><br>**Number randomised to attention control and usual care group^:** 84 (51% men, mean age 66 years, SD 14)<br><br>**Total number included in final analysis:** 111<br><br>**Number included in treatment group for final analysis:** 34<br><br>**Number included in control group for final analysis:** 77 |
| Interventions | **Treatment:** cognitive-behavioural therapy (techniques included education, graded task assignment, activity scheduling, and identification and modification of unhelpful thoughts and beliefs. Interventions were tailored to meet the individual's needs. Frequency and duration of sessions were 10 × 1 hour sessions over 13 weeks<br><br>**Administered by:** trained therapist<br><br>**Supervision:** therapist received training and clinical supervision by experienced cognitive therapist<br><br>**Intervention fidelity:** not reported<br>**Attention control:** no formal therapeutic intervention; conversation focused on day-to-day occurrences and discussion regarding physical effects of stroke and life changes (10 × 1 hour visits over 13 weeks)<br><br>**Control:** usual care (no contact)<br>**Duration:** 13 weeks<br><br>**Follow-up:** 3 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using BDI, WDI, GHQ 28<br>• Activities of daily living measured using EADL scale<br>• Leaving the study early |


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**Lincoln 2003** *(Continued)*

- Death

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a computer generated random number sequence was prepared in advance and sealed in opaque, consecutively numbered envelopes by an independent researcher" (p. 112) |
| Allocation concealment (selection bias) | High risk | **Quote:** "….prepared in advance and sealed in opaque, consecutively numbered envelopes by an independent researcher" (p. 112)<br>**Comment:** this method of allocation concealment can be tampered with |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** due to the nature of the intervention, it was not possible to mask participants, CBT therapists, or researchers to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Quote:** "outcome assessments were administered by an assistant psychologist, who was blind to the group allocation, 3 and 6 months after randomization. The primary outcome measures were the BDI and WDI, which were sent for patients to complete prior to a visit" (p. 112) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 5/121 (4.1%) not included in analyses |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes were reported; no trial protocol available to compare with the publication |
| Other bias | High risk | **Comment:** significantly more participants in the treatment group with an ICD-10 diagnosis of depression |

**Lipsey 1984**

| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** nortriptyline (TCA)<br>**Control arm:** matched placebo |
|---|---|
| Participants | **Geographical location:** USA<br>**Setting:** mixed<br>**Stroke criteria:** ischaemic stroke and primary intracerebral haemorrhage<br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br>**Time since stroke:** 262 ± 437 days<br>**Inclusion criteria:** (1) included outpatients who requested treatment for poststroke depressive disorder |


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**Lipsey 1984** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** (1) current treatment for depression; (2) severe comprehension deficit; (3) medical contraindication to nortriptyline<br><br>**Depression criteria:** psychiatric interview (PSE, DSM-III)<br><br>**Total number randomised in this trial:** 39<br><br>**Number randomised to treatment group:** 17<br>**Number randomised to control group:** 22<br><br>**Total number included in final analysis:** 34<br><br>**Number included in treatment group for final analysis:** 14 (64% men, mean age 62 years, SD 9)<br><br>**Number included in control group for final analysis:** 20 (65% men, mean age 60 years, SD 12) |
| Interventions | **Treatment:** nortriptyline (TCA) 20 to 100 mg daily; 2 treatment regimens combined; dose escalation over treatment period to 100 mg<br>**Control:** matched placebo<br>**Duration:** 4 to 6 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression (proportion no longer meeting entry criteria (DSM-III), measured using HDRS and ZDS)^†<br><br>**Secondary outcomes**<br><br>• Death<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "all patients were randomly assigned to nortriptyline or placebo treatment by means of a random number table" (p. 297) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "nortriptyline and placebo were supplied in identical capsules" (p. 297) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "patients and their families, clinical examiners and nursing staff were unaware of the drug treatment being given" (p. 297) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "patients and their families, clinical examiners and nursing staff were unaware of the drug treatment being given" (p. 297) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported; 5/39 (13%) not included in analyses |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |


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**Lipsey 1984** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Liu 2015**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS + citalopram (SSRI) + short-term benzodiazepines (BZDs) if needed for insomnia<br><br>**Control arm:** citalopram (SSRI) + short-term BZDs if needed for insomnia |
| Participants | **Geographical location:** China<br><br>**Setting:** mixed<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Inclusion criteria:** (1) can sign informed consent; (2) 17-item HDRS score ≥ 17<br><br>**Exclusion criteria:** (1) drug dependence history in recent 6 months; (2) bleeding tendency, severe hepatic or renal impairment, or other physical illness; (3) epilepsy history, head injury with consciousness loss history, history of cranial operation, metal implant or electronic devices in the body<br><br>**Depression criteria:** 17-item HDRS score ≥ 17<br><br>**Total number randomised in this trial:** 60<br><br>**Number included in treatment group:** 30 (56% men; mean age 64.2, SD 3.1)<br><br>**Number included in control group:** 30 (53% men; mean age 65.1, SD 3.5)<br><br>**Total number included in final analysis:** 60<br><br>**Number included in treatment group for final analysis:** 30<br><br>**Number included in control group for final analysis:** 30 |
| Interventions | **Treatment:** rTMS + citalopram (SSRI), starting from 10 mg/d in the morning, may titrate up to 20 mg/d according to the patient's condition + short-term BZDs (only for difficulty in falling asleep; combined duration: less than 1 week). Frequency: 10 Hz, intensity: 80% resting motor threshold, 1 stimulation lasts 5 seconds and stops for 20 seconds, total treatment time: 20 minutes, 1 treatment per day, 5 treatments a week, total 4 weeks, location: left DLPFC<br><br>**Control:** citalopram (SSRI) + short-term BZDs<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcome**<br><br>• Depression measured using 17-item HDRS<br><br>**Secondary outcome** |


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**Liu 2015** *(Continued)*

- Impairment measured using NIHSS

| Notes | |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Lu 2016**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS + duloxetine (SNRI) + ischaemic stroke routine care<br>**Control arm:** duloxetine (SNRI) + ischaemic stroke routine care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br>**Inclusion criteria:** (1) clear consciousness; (2) 24-item HDRS score ≥ 20; (3) meeting diagnostic criteria of ICD-10 for depression<br>**Exclusion criteria:** (1) cognitive impairment; (2) no language impairment; (3) severe cardiac or pulmonary disease, hepatic or renal impairment; (4) bleeding tendency<br>**Depression criteria:** meeting diagnostic criteria of ICD-10 for depression and 24-item HDRS score ≥ 20 |


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**Lu 2016** *(Continued)*

| | |
|---|---|
| | **Total number randomised in this trial:** 80<br><br>**Number randomised to treatment group:** 40 (57.5% men; mean age 65.3, SD 8.8)<br><br>**Number randomised to control group:** 40 (52.5% men; mean age 63.8, SD 8.4)<br><br>**Total number included in final analysis:** 73<br><br>**Number included in treatment group for final analysis:** 36<br><br>**Number included in control group for final analysis:** 37 |
| Interventions | **Treatment:** rTMS + duloxetine (SNRI) 60 mg/d + ischaemic stroke routine care. Frequency: 3.0 Hz, intensity: 110% resting motor threshold, 1 treatment lasts 5 minutes, 5 treatments a week, location: left temporoparietal area<br><br>**Control:** duloxetine (SNRI) + ischaemic stroke routine care<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using MADRS<br>• Depression measured using 24-item HDRS<br>• Dependence measured using SDS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random numbers table used for sequence generation |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 7/80 not included in the analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |


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**Meng 2015**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS<br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** brain CT or MRI confirmed cerebral infarct<br>**Inclusion criteria:** (1) normal expression ability; (2) first stroke; (3) clear consciousness, can sign informed consent, right-handedness; (4) HDRS score ≥ 8<br>**Exclusion criteria:** (1) history of psychiatric illness; (2) cerebral haemorrhage, history of epilepsy, contraindication for TMS, not finishing treatment course<br>**Depression criteria:** HDRS score ≥ 8<br>**Total number randomised in this trial:** 108<br>**Number randomised to treatment group:** 54 (62.9% men; mean age 64.2, SD 4.2)<br>**Number randomised to control group:** 54 (64.8% men; mean age 65.8, SD 4.0)<br>**Total number included in final analysis:** 108<br>**Number included in treatment group for final analysis:** 54<br>**Number included in control group for final analysis:** 54 |
| Interventions | **Treatment:** rTMS + usual care (which includes antidepressants if already on them, no change of antidepressant dosage or medication during treatment). Frequency: 10 Hz, intensity: 80% motor threshold, 1 stimulation lasts 4.9 seconds and stops for 20 seconds, 86 cycles a day, total 1960 impulses a day, location: left DLPFC<br>**Control:** sham rTMS, keeping coils at 90-degree angles with the scalp + usual care (which includes antidepressants if already on them, no change in antidepressant dosage or medication during treatment)<br>**Duration:** 2 weeks<br>**Follow-up:** 4 weeks |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Disability measured using BI<br>• Impairment measured using CSS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random numbers table used for sequence generation |


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**Meng 2015** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** significant differences in age between groups |

**Mitchell 2002**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** cognitive-behavioural therapy plus problem-solving<br>**Control arm:** written information from the Stroke Association including information about depression |
| Participants | **Geographical location:** USA<br>**Setting:** outpatient<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** verified by CT or MRI<br>**Time since stroke:** within 4 months<br>**Inclusion criteria:** (1) stroke within 4 months; (2) 21 years of age and older<br>**Exclusion criteria:** (1) subarachnoid or intracranial haemorrhagic stroke; (2) global aphasia; (3) reduced level of consciousness (GCS < 15)<br>**Depression criteria:** diagnosis of depression validated by the Diagnostic Interview and Structured Hamilton among those who scored > 10 on the GDS<br>**Total number randomised in this trial:** 101<br>**Number randomised to treatment group:** 48 (60% men, mean age 57 years, age range 25 to 88 years)<br>**Number randomised to control group:** 53 (60% men, mean age 57 years, age range 29 to 88 years)<br>**Total number included in final analysis:** 92<br>**Number included in treatment group for final analysis:** 44<br>**Number included in control group for final analysis:** 48 |


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**Mitchell 2002** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** cognitive-behavioural therapy plus problem-solving. Sessions were focused on the individual; however, a participant could opt to have a family member or an informal caregiver join these sessions. The brief psychosocial–behavioural intervention was adapted from the "Seattle Protocols" shown to reduce disability associated with depression in Alzheimer disease. All participants received written information from the Stroke Association including information about depression. Participants could receive antidepressant medication at the discretion of their usual care provider. Frequency and duration: 9 sessions over 8 weeks<br><br>**Administered by:** therapists<br><br>**Supervision:** all therapists met monthly with the clinical psychologist who developed the intervention<br><br>**Intervention fidelity:** sessions were audio-taped, and session content was compared to the content specified for each visit<br>**Control:** all participants received written information from the Stroke Association including information about depression. Participants could receive antidepressant medication at the discretion of their usual care provider<br>**Duration:** 8 weeks<br><br>**Follow-up:** 12 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Adverse event data systematically collected included worsening of depression, suicidal ideation, and suicide attempts |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "randomization status was generated by a computerized adaptive randomisation procedure…" (p. 3075) |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** due to the nature of the trial, it was not possible to mask participants, clinicians, and researchers to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "all outcome assessors were masked to the participant's randomization status at each data collection point. We did not detect any breaches in masking" (p. 3075) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** 9/101 participants were not included in the analysis (per protocol analysis reported only) |
| Selective reporting (reporting bias) | High risk | **Comment:** caregiving burden and benefit (Sense of Competence Scale) outcome in the protocol not reported in the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |


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**Murray 2002**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** sertraline (SSRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Sweden<br>**Setting:** mixed<br><br>**Stroke criteria:** all subtypes<br><br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br><br>**Time since stroke:** 12 months<br><br>**Inclusion criteria:** (1) > 17 years of age; (2) stroke within previous 12 months<br><br>**Exclusion criteria:** (1) under 18 years of age; (2) severely impaired communication; (3) apparent difficulties in adhering to study protocol; (4) acute myocardial infarction; (5) psychiatric illness other than depression; (6) significant risk of suicide; (7) antidepressants during the month before randomisation; (8) current use of psychotropic medication or opiate analgesic drugs; (9) < 20% reduction in MADRS score at 6 weeks<br><br>**Depression criteria:** psychiatric interview (DSM-IV, major and minor) and MADRS > 9<br><br>**Total number randomised in this trial:** 123<br><br>**Number randomised to treatment group:** 62 (52% men, mean age 71 years, SD 10)<br>**Number randomised to control group:** 61 (44% men, mean age 71 years, SD 10)<br><br>**Total number included in final analysis:** 123<br><br>**Number included in treatment group for final analysis:** 62<br><br>**Number included in control group for final analysis:** 61 |
| Interventions | **Treatment:** sertraline (SSRI) 50 mg daily; possible dose escalation to 100 mg after 4 weeks<br>**Control:** matched placebo<br>**Duration:** 26 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using MADRS (change in scores from baseline to end of treatment on MADRS)<br><br>**Secondary outcomes**<br><br>• Death<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a centralised randomization procedure was applied. The Central Pharmacy in Stockholm kept the randomization list" (p. 709) |


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**Murray 2002** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | **Quote:** "each centre pharmacy received a consecutive series of presealed treatment packages" (p. 709) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "patients received double-blind identical capsules of either sertraline 50 mg or placebo, once a day as a starting dose" (p. 709) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** double-blind placebo-controlled trial, which suggests that outcome assessors were blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Quote:** "efficacy analyses were based on the intention to treat (ITT), last observation carried forward population…" (p. 710)<br>"… response and remission rates were calculated for those patients who completed the study" (p. 710)<br>**Comment:** continuous outcomes analysed by ITT; dichotomous outcomes analysed per protocol (data reported for 38/62, 61% intervention participants; 31/61, 51% control participants) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** significant trend towards more left hemisphere lesion strokes in treatment group |

**Ohtomo 1991**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** Aniracetam (nootropic agent)<br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Japan<br>**Setting:** unclear<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** not reported<br>**Time since stroke:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** not reported<br>**Depression criteria:** based on physician's impression, no scale used for evaluation<br>**Total number randomised in this trial:** 285<br>**Number randomised to treatment group:** 150 (details unclear)<br>**Number randomised to control group:** 135 (details unclear)<br>**Total number included in final analysis:** 206 |


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**Ohtomo 1991** *(Continued)*

| | |
|---|---|
| | **Number included in treatment group for final analysis:** unclear<br><br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** Aniracetam (nootropic agent) 600 mg twice daily<br>**Control:** matched placebo<br>**Duration:** 12 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression measured by physician assessment of change in depression from baseline to end of treatment<br>• Anxiety measured by physician assessment of change |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | **Comment:** generation sequence controlled by Professor Furukawa |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Comment:** double-blind reported and matched placebo used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** double-blind reported, so likely that outcome assessment was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analyses reported only; 79/285 (27.3%) missing from depression analyses |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported. No trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** differences in baseline demographics between groups not reported |

**Ponzio 2001**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** paroxetine (SSRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Italy |


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**Ponzio 2001** *(Continued)*

| | |
|---|---|
| | **Setting:** outpatient<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) 18 to 85 years of age; (2) MMSE score > 23<br><br>**Exclusion criteria:** (1) concurrent predominant psychiatric disorders; (2) receiving psychotropic pharmacotherapy; (3) with substance abuse/dependence; (4) participation in other clinical trials; (5) suicide risk; (6) concomitant medication intolerance to paroxetine<br><br>**Depression criteria:** MADRS > 18<br><br>**Total number randomised in this trial:** 229<br><br>**Number randomised to treatment group:** 112 (54% men, mean age 64 years, SD 11)<br>**Number randomised to control group:** 117 (55% men, mean age 66 years, SD 11)<br><br>**Total number included in final analysis:** 229<br><br>**Number included in treatment group for final analysis:** 112<br><br>**Number included in control group for final analysis:** 117 |
| Interventions | **Treatment:** paroxetine (SSRI) 20 to 40 mg daily<br>**Control:** matched placebo<br>**Duration:** 8 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression (change in scores from baseline to end of treatment) measured using MADRS and CGI<br><br>**Secondary outcomes**<br><br>• Proportion scoring < 7 on MADRS and responders on CGI<br>• Disability (change in scores from baseline to end of treatment) measured using BI<br>• Functional capacity (change in scores from baseline to end of treatment) measured using Rankin scale<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Quote:** "subjects randomised to paroxetine…" (p. 1)<br><br>**Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Quote:** "blinding of study medication was maintained by referring to dosage…" (p. 1)<br><br>**Comment:** in study design, it states that this study is a 'double-blind, placebo-controlled' trial, but in treatment, this is a 'single-blind placebo' trial |


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**Ponzio 2001** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | **Comment:** in study design, it states that this is a 'double-blind, placebo controlled' trial, but in treatment, this is a 'single-blind placebo' trial |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | **Quote:** "the primary analysis (post stroke depression) population was the intention-to-treat (ITT) population…." (p. 1) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Rampello 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** reboxetine (NRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** Italy<br>**Setting:** outpatient<br>**Stroke criteria:** single ischaemic or haemorrhagic stroke<br><br>**Method of stroke diagnosis:** diagnosis via CT and MRI<br><br>**Time since stroke:** 2 weeks<br><br>**Inclusion criteria:** (1) presence of major or minor depression; (2) presence of retarded depression; (3) lack of treatment with antidepressants 2 weeks before randomisation; (4) absence of treatment with neuroleptic drugs during 3 months before enrolment; (5) can sign informed consent<br><br>**Exclusion criteria:** (1) previous degenerative or expansive neurological disease; (2) tumour, multiple sclerosis, amyotrophic sclerosis, hydrocephalus, SAH, Binswanger's disease; (3) history of psychiatric illness (other than depression); (4) severe aphasia; (5) severe cognitive deficit; (6) chronic alcoholism<br><br>**Depression criteria:** psychiatric interview, HDRS > 20, BDI > 15<br><br>**Total number randomised in this trial:** 31<br><br>**Number randomised to treatment group:** 16 (44% men, mean age 78 years, SD 4)<br>**Number randomised to control group:** 15 (46% men, mean age 77 years, SD 4)<br><br>**Total number included in final analysis:** 31<br><br>**Number included in treatment group for final analysis:** 16<br><br>**Number included in control group for final analysis:** 15 |
| Interventions | **Treatment:** reboxetine (NRI) 4 mg twice daily<br>**Control:** matched placebo<br>**Duration:** 16 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes** |


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**Rampello 2005** *(Continued)*

- Depression measured using HDRS and BDI

**Secondary outcomes**

- Adverse events

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a computer-generated randomization was carried out by a physician who was not involved in the evaluation of patients…" (p. 277) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "the generator of randomization assigned a code number (0) to patients who were treated with reboxetine, and a different code (1) was given to patients treated with placebo. Code 0 was stuck on totally white boxes, without any marks, sealed, containing the tablets of..." (p. 278) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "the generator of randomization handed over, for each patient, the box marked with the code and containing the tablets that should be taken" (p. 279)<br>**Comment:** participants were blinded but the personnel who delivered the intervention knew the treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "the other physician was in charge of the follow-up visits and of the evaluation of the outcome measures" (p. 279) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** follow-up of all participants was complete; ITT analysis reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol to compare with the publication |
| Other bias | Low risk | |

**Reding 1986**

Methods

**Study design:** parallel design

**Number of arms:** 2

**Experimental arm:** trazodone-HCl (TCA)

**Control arm:** matched placebo

Participants

**Geographical location:** USA
**Setting:** inpatients
**Stroke criteria:** all subtypes

**Method of stroke diagnosis:** diagnosis via clinical signs and CT (% not reported)

**Time since stroke:** 45 to 48 days

**Inclusion criteria:** not reported


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**Reding 1986** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** (1) myocardial infarction within previous month; (2) on antiarrhythmic medication<br><br>**Depression criteria:** psychiatric interview (DSM-III, major and minor)<br><br>**Total number randomised in this trial:** 17<br><br>**Number randomised to treatment group:** 11 (66% men, mean age 68 years, SE 2)<br>**Number randomised to control group:** 6 (73% men, mean age 68 years, SE 3)<br><br>**Total number included in final analysis:** 17<br><br>**Number included in treatment group for final analysis:** 11<br><br>**Number included in control group for final analysis:** 6 |
| Interventions | **Treatment:** trazodone-HCl (TCA) 50 mg daily; dose escalation every 3 days to target dose of 200 mg<br>**Control:** matched placebo<br>**Duration:** 32 ± 6 days (treatment group) and 24 ± 4 days (control group)<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using clinical diagnosis of depression and ZDS<br><br>**Secondary outcomes**<br><br>• Disability measured using BI |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "patients were assigned to either treatment or placebo groups according to a table of random numbers" (p. 763) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "…or placebo in an identical capsule was administered orally…" (p. 763) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "…or placebo in an identical capsule was administered orally…" (p. 763) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Quote:** "if the attending physician, unaware of treatment group assignment…." (p. 764) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** follow-up of all participants was complete; ITT analysis reported in table |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol to compare with the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information not reported |


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**Robinson 2008a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** nefiracetam (nootropic agent)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** USA<br>**Setting**: unclear<br><br>**Stroke criteria:** ischaemic and primary intracerebral haemorrhage<br><br>**Method of stroke diagnosis:** unclear<br><br>**Time since stroke:** 10 days to 3 months<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) other psychiatric or neurological disease (e.g. Alzheimer's disease, Parkinson's disease); (2) depression or suicidal plans requiring psychiatric hospitalisation; (3) on psychotropic medication (excluding benzodiazepines or insomnia medication); (4) comprehension deficit precluding verbal interview; (5) life-threatening illness; (6) previous subarachnoid haemorrhage<br><br>**Depression criteria:** psychiatric interview to confirm DSM-IV diagnosis of "depression due to stroke with major depressive-like episode" plus HDRS score ≥ 18<br><br>**Total number randomised in this trial:** 76<br><br>**Number randomised to treatment group:** 48 (40% men; mean age 68.1, SD 11.9)<br><br>**Number randomised to control group:** 28** (54% men; mean age 66.8, SD 13.0)<br><br>**Total number included in final analysis:** 66<br><br>**Number included in treatment group for final analysis:** 41<br><br>**Number included in control group for final analysis:** 25** |
| Interventions | **Treatment:** nefiracetam (nootropic agent) 900 mg, 3 × 150 mg capsule twice/d<br><br>**Control:** matching placebo 3 × 150 mg capsule twice/d<br><br>**Duration:** 12 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Depression measured using BDI<br><br>**Secondary outcomes**<br><br>• Apathy measured using Apathy Scale<br>• Leaving the trial early<br>• Adverse events |
| Notes | |
| ***Risk of bias*** | |


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**Robinson 2008a** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** based on the study author's responses, sequence generation was attained with computer-generated numbers |
| Allocation concealment (selection bias) | Low risk | **Quote:** "nefiracetam or placebo was administered double-blind in three identical 150 mg capsules…" (p. 179) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Comment:** study author states that this study was double-blinded but does not state who was blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** study author states that this study was double-blinded but does not state who was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Quote:** "...missing data points were estimated using LOCF..." (p. 146)<br>"attrition related bias cannot be ruled out" (p. 149)<br><br>**Comment:** the number of dropouts reported and the number analysed are inconsistent within and between publications |
| Selective reporting (reporting bias) | High risk | **Comment:** study author reports that a number of measures were assessed but does not provide details of these measures in the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information was not reported |

**Robinson 2008b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** nefiracetam (nootropic agent)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** USA<br>**Setting**: unclear<br><br>**Stroke criteria:** ischaemic and primary intracerebral haemorrhage<br><br>**Method of stroke diagnosis:** unclear<br><br>**Time since stroke:** 10 days to 3 months<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) other psychiatric or neurological disease (e.g. Alzheimer's disease, Parkinson's disease); (2) depression or suicidal plans requiring psychiatric hospitalisation; (3) on psychotropic medication (excluding benzodiazepines or insomnia medication); (4) comprehension deficit precluding verbal interview; (5) life-threatening illness; (6) previous subarachnoid haemorrhage<br><br>**Depression criteria:** psychiatric interview to confirm DSM-IV diagnosis of "depression due to stroke with major depressive-like episode" plus HDRS score ≥ 18<br><br>**Total number randomised in this trial:** 83 |


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**Robinson 2008b** *(Continued)*

| | |
|---|---|
| | **Number included in treatment group:** 55 (40% men; mean age 64.7, SD 11.9)<br>**Number included in control group:** 28** (54% men; mean age 66.8, SD 13.0)<br>**Total number included in final analysis:** 72<br>**Number included in treatment group for final analysis:** 47<br>**Number included in control group for final analysis:** 25** |
| Interventions | **Treatment:** nefiracetam 600 mg, 3 × 150 mg capsule twice/d<br>**Control:** matching placebo 3 × 150 mg capsule twice/d<br>**Duration:** 12 weeks<br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Depression measured using BDI<br>**Secondary outcomes**<br>• Apathy measured using Apathy Scale<br>• Leaving the trial early<br>• Adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** based on the study author's responses, sequence generation was attained with computer-generated numbers |
| Allocation concealment (selection bias) | Low risk | **Quote:** "nefiracetam or placebo was administered double-blind in three identical 150 mg capsules…" (p. 179) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Comment:** study author states that this study was double-blinded but does not state who was blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** study author states that this study was double-blinded but does not state who was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Quote:** "...missing data points were estimated using LOCF..." (p. 146)<br>"attrition related bias cannot be ruled out" (p. 149)<br>**Comment:** the number of dropouts reported and the number analysed are inconsistent within and between publications |
| Selective reporting (reporting bias) | High risk | **Comment:** study author reports that a number of measures were assessed but does not provide details of these measures in the publication |
| Other bias | Unclear risk | **Comment:** baseline demographic information was not reported |


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**Sun 2013**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS + Deanxit (flupentixol and melitracen)<br><br>**Control arm:** Deanxit (flupentixol and melitracen) |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Time since stroke:** 8 days<br><br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) clear consciousness, no obvious aphasia or comprehension impairment; (3) no severe cardiac disease history; (4) first stroke or previous stroke without sequelae; (5) internal carotid system cerebral infarct, no epilepsy or head injury history, can sign informed consent<br><br>**Exclusion criteria:** (1) cerebral haemorrhage, progressive stroke, intracranial infection, intracranial tumour, seizure attack or consciousness disturbance, severe cardiac event (heart function class ≥ 3), pulmonary (respiratory failure) and renal (uremia) impairment, mental implant in the body (e.g. pacemaker, metal stent), pregnancy or children<br><br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression<br><br>**Total number randomised in this trial:** 100<br><br>**Number randomised to treatment group:** 50 (78% men, mean age 64.6, SD 11.4)<br><br>**Number randomised to control group:** 50 (68% men, mean age 66.5, SD 11.1)<br><br>**Total number included in final analysis:** 100<br><br>**Number included in treatment group for final analysis:** 50<br><br>**Number included in control group for final analysis:** 50 |
| Interventions | **Treatment:** rTMS + Deanxit (flupentixol and melitracen), 10.5 mg/d in the morning, starting on day 8 after stroke onset. Frequency: 1 Hz, intensity: 90% motor threshold, 30 stimulations for 1 series, 1 series a day, location: bilateral pre-frontal area, starting on day 8 after stroke onset<br><br>**Control:** Deanxit (flupentixol and melitracen)<br><br>**Duration:** 2 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Depression measured using SDS |
| Notes | |
| ***Risk of bias*** | |


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**Sun 2013** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Thomas 2007**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** behavioural psychotherapy<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** UK<br>**Setting:** mixed<br><br>**Stroke criteria**: unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Time since stroke:** 8.85 days<br><br>**Inclusion criteria:** (1) presence of aphasia confirmed by a speech and language therapist (hospital or community participants) or using the Sheffield Screening Test for Acquired Language Disorders (voluntary sector participants)<br><br>**Exclusion criteria:** (1) receiving treatment for depression pre-stroke (at the time of stroke), (2) with dementia, (3) blind or deaf; (4) unable to speak English before stroke<br><br>**Depression criteria:** using the 'sad' item of the VAMS and the 10-item hospital version of the SAD-Q, completed by a nurse, relative, or carer. Those identified as having low mood on the 'sad' item of the VAMS (cut-off > 50) or the SAD-Q (cut-off > 6)<br><br>**Total number randomised in this trial:** 105<br><br>**Number randomised to treatment group:** 51 (57% men, mean age 68.5 years, SD 13.1) |


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**Thomas 2007** *(Continued)*

| | |
|---|---|
| | **Number randomised to control group:** 54 (69% men, mean age 65.5 years, SD 13.9)<br><br>**Total number included in final analysis:** 89<br><br>**Number included in treatment group for final analysis:** 43<br><br>**Number included in control group for final analysis:** 46 |
| Interventions | **Treatment 1:** behavioural psychotherapy up to 20 sessions of treatment over 3 months, with each session lasting approximately 1 hour. The manual had been developed from studies of cognitive-behavioural therapy for depression after stroke and with older adults, and from guidelines on conducting cognitive-behavioural therapy with people with aphasia. The intensity of therapy was left to the discretion of the assistant psychologist. The intervention was tailored to the individual's needs, and communication resources such as pictures, photographs, and letter charts were used<br><br>**Administered by:** assistant psychologist<br><br>**Supervision:** therapy was delivered by an assistant psychologist supervised weekly by a clinical psychologist. All assistant psychologists attended a joint monthly supervision meeting with a consultant clinical neuropsychologist. Assistant psychologists received training in supported communication from speech and language therapists and were provided with a therapy manual<br><br>**Intervention fidelity:** delivery of therapy was monitored by observation of therapy sessions by the chief investigator. The content of therapy was documented using record forms completed by the assistant psychologist after each session<br><br>**Control:** usual care<br>**Duration:** 3 months<br><br>**Follow-up:** 3 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using the 21-item hospital version of the SAD-Q – an observational measure of mood completed by a relative or primary carer<br>• Depression measured using the 'sad' item of VAMS<br><br>**Secondary outcomes**<br><br>• Self-esteem measured using Visual Analogue Self-Esteem Scale<br>• Activities of daily measured using Nottingham Leisure Questionnaire<br>• Caregiver strain measured using CSI<br>• Patient and carer satisfaction with care measured using 100-mm VAS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "participants were randomly allocated to one of two groups…..using a computer generated pseudo-random list…" (p. 400) |
| Allocation concealment (selection bias) | Low risk | **Quote:** "the assistant psychologist providing treatment accessed the allocation by logging into a secure computer server, thus ensuring concealment of allocation" (p. 400) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** due to the nature of the trial, not possible to mask participants, personnel, and researchers to treatment allocation |


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**Thomas 2007** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | **Comment:** primary endpoint self-assessed by relative or carer who was aware of treatment allocation. Secondary endpoints assessed using a blinded assessor |
| Incomplete outcome data (attrition bias) All outcomes | High risk | **Quote:** "outcomes were analysed by intention to treat" (p. 401)<br>"...missing data using the last observation carried forward on the assumption of no change…" (p. 402)<br>**Comment:** only per protocol analysis reported |
| Selective reporting (reporting bias) | High risk | **Comment:** one secondary outcome measure (Extended Activities of Daily Living Scale) not reported in the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Towle 1989**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** pragmatic approach (counselling)<br>**Control arm:** custom-designed information booklet |
| Participants | **Geographical location:** UK<br>**Setting:** outpatients<br>**Stroke criteria:** all subtypes<br>**Method of stroke diagnosis:** diagnosis via clinical signs<br>**Time since stroke:** 6 to 7 months<br>**Inclusion criteria:** (1) able to complete questionnaires unaided<br>**Exclusion criteria:** (1) stroke < 1 year before randomisation; (2) residence in hospital or residential care<br>**Depression criteria:** WDI score > 17 or GHQ-28 score > 9<br>**Total number randomised in this trial:** 44<br>**Number randomised to treatment group:** 21 (43% men, mean age 70 years, SD 9)<br>**Number randomised to control group:** 23 (30% men, mean age 69 years, SD 7)<br>**Total number included in final analysis:** 43<br>**Number included in treatment group for final analysis:** 21<br>**Number included in control group for final analysis:** 22 |
| Interventions | **Treatment:** pragmatic approach dealing with problems identified by social worker and patients; included counselling the patient and caregiver, giving opportunity to reflect upon their situation and express their feelings (duration: 2 to 11 visits over 16 weeks, mean visits 6.8 ± 2.8; however, length and content of visits varied)<br>**Administered by:** not reported<br>**Supervision:** not reported |


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**Towle 1989** *(Continued)*

| | |
|---|---|
| | **Intervention fidelity:** unclear; no report of formal evaluation of the quality or content of therapy provided<br>**Control:** custom-designed information booklet (covered areas believed to be of use and interest to stroke survivors and their families, such as details on housing and financial benefits; aids to daily living; addresses of stroke clubs and self-help groups; telephone number of local social services department), 1 visit, no ongoing visits<br>**Administered by:** social worker<br><br>**Duration:** 16 weeks<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcomes**<br><br>• Depression (change in scores from baseline to end of treatment) measured using WDI and GHQ-28 |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "the order of the envelopes had been decided before the study using random number tables" (p. 520) |
| Allocation concealment (selection bias) | High risk | **Quote:** "the patients were then allocated randomly to one of two groups using sealed envelopes each containing a slip of paper stating either "treatment" or "no treatment"" (p. 520) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "the patients were then allocated randomly to one of two groups using sealed envelopes each containing a slip of paper stating either "treatment" or "no treatment"" (p. 520)<br><br>**Comment:** due to the nature of the trial, it was not possible to mask participants or social worker to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Quote:** "each patient was visited 8 weeks and 16 weeks later by the independent assessor who repeated the pre-intervention questionnaires"<br><br>**Comment:** it is unclear whether the independent assessor was blinded to treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** 1/44 participants was excluded from the analysis; only per protocol analysis reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Wang 2004a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** psychological therapy |


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**Wang 2004a** *(Continued)*

| | |
|---|---|
| | **Control arm:** usual care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria**: not reported<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995 and confirmation by brain CT<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) first-ever stroke<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) previous neurological disease or uncooperative with examination<br><br>**Depression criteria:** psychiatric interview to confirm diagnosis meets depression diagnostic criteria of the CCMD-2-R<br><br>**Total number randomised in this trial:** 70<br><br>**Number randomised to treatment group:** 35 (57% men; mean age 56, SD 8)<br><br>**Number randomised to control group:** 35 (54% men; mean age 56, SD 7)<br><br>**Total number included in final analysis:** 70<br><br>**Number included in treatment group for final analysis:** 35<br><br>**Number included in control group for final analysis:** 35 |
| Interventions | **Treatment:** psychological therapy 1 hour twice/week administered by a psychiatrist. Psychological therapy entailed psychological support and explanation, relaxing training, and music therapy<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** usual care<br><br>**Duration:** 5 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using ZDS<br>• Cognition measured by P300 |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |


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**Wang 2004a** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Wang 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** fluoxetine (SSRI)<br>**Control arm:** matched placebo |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** all stroke<br>**Method of stroke diagnosis:** diagnosis consistent with Diagnostic Criteria for Cerebrovascular Disease formulated by the Fourth National Conference of Chinese Medical Association in 1995<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** (1) history of psychiatric illness; (2) dementia; (3) aphasia; (4) disturbance of consciousness<br>**Depression criteria:** HDRS scores > 17<br>**Total number randomised in this trial:** 108<br>**Number randomised to treatment group:** 54 (57% men, mean age 58.9 years for total sample)<br>**Number randomised to control group:** 54 (57% men, mean age 58.9 years for total sample)<br>**Total number included in final analysis:** 108<br>**Number included in treatment group for final analysis:** 54<br>**Number included in control group for final analysis:** 54 |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 to 40 mg/d. If reduction in HDRS scores ≤ 5 points after 2 weeks of treatment, increase dosage to 40 mg/d |


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**Wang 2005** *(Continued)*

| | |
|---|---|
| | **Control:** matched placebo<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS (remission: no depression symptoms and HDRS < 7; improved depression symptoms: reduction of HDRS scores by ≥ 5; ineffective: severely depressed mood and reduction in HDRS scores < 4)<br><br>**Secondry outcomes**<br><br>• Neurological Impairment measured using CSS<br>• Leaving the trial early |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment**: method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment**: method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment**: single-blind reported but who was blinded not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** ITT (last observation carried forward) for dichotomous endpoints; unclear for continuous endpoints |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Unclear risk | **Comment:** difference in baseline demographic characteristics not reported |

**Wang 2005a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** combined psychotherapy + paroxetine (SSRI)<br><br>**Control arm:** paroxetine (SSRI) |
| Participants | **Geographical location:** China |


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**Wang 2005a** *(Continued)*

| | |
|---|---|
| | **Setting:** inpatient<br><br>**Stroke criteria:** ischaemic and haemorrhagic stroke; haemorrhagic subtypes not specified<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for cerebrovascular disease formulated by the National Symposium on Cerebrovascular Disease of Chinese Medical Association in 1995 and confirmation by brain CT or MRI<br><br>**Time since stroke:** 21.85 days<br><br>**Inclusion criteria:** (1) first-ever stroke<br><br>**Exclusion criteria:** (1) history of psychiatric illness, depressive phase of bipolar disorders; (2) antidepressants and antipsychotics in the previous 3 months; (3) severe cognitive impairment, aphasia; (4) severe cardiac impairment, hepatic or renal impairment; (5) coma; (6) too severe clinical condition to receive interview; (7) allergy to paroxetine<br><br>**Depression criteria:** meeting both organic depression and organic anxiety diagnostic criteria of the CCMD-3<br><br>**Total number randomised in this trial:** 54<br><br>**Number included in treatment group:** 27 (52% men; mean age 64.0, SD 5.3)<br><br>**Number included in control group:** 27 (52% men; mean age 62.4, SD 6.1)<br><br>**Total number included in final analysis:** 54<br><br>**Number included in treatment group for final analysis:** 27<br><br>**Number included in control group for final analysis:** 27 |
| Interventions | **Treatment:** combined psychotherapy, 1 session/week variable length 30 to 60 minutes administered by a psychotherapist + SSRI (paroxetine) 20 mg/d in the morning. Psychotherapy was described as having a supportive focus<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** paroxetine (SSRI) 20 mg/d in the morning<br><br>**Duration:** 6 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Anxiety measured using HARS<br>• Disability measured using BI<br>• Impairment measure using SSS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Wang 2005a** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment**: method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment**: method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment**: blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | **Comment:** 2/54 treatment and 0/54 control dropped out. ITT for categorical outcome variable: clinical efficacy of participants with missing data regarded as ineffective; analysis by allocation for continuous outcomes analysis not reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Watkins 2007**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** motivational interviewing<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** UK<br>**Setting:** inpatient<br><br>**Stroke criteria:** all subtypes<br><br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br><br>**Time since stroke:** 5 to 28 days<br><br>**Inclusion criteria:** (1) over 18 years of age<br><br>**Exclusion criteria:** (1) severe cognitive and communication problems; (2) moving out of the area after discharge; (3) already receiving psychiatric or clinical psychology intervention<br><br>**Depression criteria:** GHQ score > 4<br><br>**Total number randomised in this trial:** 254<br><br>**Number randomised to treatment group:** 127 (52% men, mean age 68 years, SD 12)<br>**Number randomised to control group:** 127 (53% men, mean age 68 years, SD 12)<br><br>**Total number included in final analysis:** 254<br><br>**Number included in treatment group for final analysis:** 127 |


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**Watkins 2007** *(Continued)*

| | |
|---|---|
| | **Number included in control group for final analysis:** 127 |
| Interventions | **Treatment:** motivational interviewing, up to 4 sessions, 1 per week, with same therapist<br><br>**Administered by:** therapists<br><br>**Supervision:** therapists received 4 days of training in motivational interviewing by a specialist followed by up to 10 practice sessions until competent and confident of the technique. Therapists were supervised by a clinical psychologist through team meetings and 1-to-1 clinical supervision sessions on a monthly basis with additional informal support throughout the study<br><br>**Intervention fidelity:** therapy sessions were audio recorded. The quality of the application of motivational interviewing was assessed by analysing a purposive sample of 60 sessions from different patients. A clinical psychologist reviewed the content of 20 therapist utterances around the midpoint of each session using a structured evaluation tool, "Motivational Interviewing Skill Code (version 2)". Utterances rated motivational interviewing-consistent included open questions, reflections, advise with permission, affirm, emphasise control, reflect, re-frame, and support. Utterances rated motivational interviewing-inconsistent included advise without permission, confront, direct, raise concern without permission, and warn. The percentage of motivational interviewing-consistent utterances was determined (total MI-consistent/(total MI-consistent plus MI-inconsistent)). Unclear if or how this information was fed back to therapists<br>**Control:** usual care<br>**Delivered by:** nurses and non-clinical psychologists<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression (proportion no longer meeting study criteria for depression, change in scores from baseline to end of treatment) measured using GHQ-28<br>• Disability measured using BI<br>• Stroke Impairment measured using Stroke Expectations Questionnaire |
| Notes | Additional unpublished data provided by study authors |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Quote:** "a research nurse randomized patients (1:1 ratio) to either usual care (control) or MI (intervention) using minimization over sex, age (65 and 65 years), baseline function in activities of daily living (ADL; Barthel: 18 to 20; 11 to 17; 0 to 10), and location (acute stroke unit)" |
| Allocation concealment (selection bias) | High risk | **Quote:** "the same nurse then assigned intervention group patients to 1 of 4 therapists using an opaque sealed envelope in a pseudorandomized blocked design" (p. 1957) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Quote:** "the same nurse then assigned intervention group patients to 1 of 4 therapists using an opaque sealed envelope in a pseudorandomized blocked design" (p. 1957)<br><br>**Comment:** due to the nature of the intervention, it was not possible to mask participants, nurses, and researchers to treatment allocation |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | **Quote:** "surviving patients were sent a questionnaire. Patients not returning questionnaires within 2 weeks were telephoned by a second research nurse, blind to group allocation, and given the option of declining, having a further |


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**Watkins 2007** *(Continued)*

| | | |
|---|---|---|
| | | questionnaire posted, completing the questionnaire over the telephone, or receiving a home visit to assist" (p. 1957) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Quote:** "where data were missing, imputations were performed as described previously" (p. 1958)<br><br>**Comment:** ITT analysis reported |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported. No trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Wiart 2000**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** fluoxetine (SSRI)<br><br>**Control arm:** matched placebo |
| Participants | **Geographical location:** France<br>**Setting:** not reported<br><br>**Stroke criteria:** ischaemic stroke and primary intracerebral haemorrhage<br><br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT (100%)<br><br>**Time since stroke:** 48 days<br><br>**Inclusion criteria:** (1) all antidepressant or neuroleptic drugs stopped 10 days before enrolment<br><br>**Exclusion criteria:** (1) severe psychiatric problems that required hospitalisation; (2) severe cognitive impairment; (3) chronic alcoholism; (4) chronic associated handicapping pathology; (5) contraindication to fluoxetine<br><br>**Depression criteria:** psychiatric interview (ICD-10 criteria) and MADRS score > 19<br><br>**Total number randomised in this trial:** 31<br><br>**Number randomised to treatment group:** 16 (56% men, mean age 66 years, SD 7)<br>**Number randomised to control group:** 15 (40% men, mean age 69 years, SD 12)<br><br>**Total number included in final analysis:** 31<br><br>**Number included in treatment group for final analysis:** 16<br><br>**Number included in control group for final analysis:** 15 |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg daily<br>**Control:** matched placebo<br>**Duration:** 45 days<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes** |


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**Wiart 2000** *(Continued)*

- Depression (change in scores from baseline to end of treatment, 50% reduction in score) measured using MADRS

**Secondary outcomes**

- Functional capacity measured using FIM
- Cognitive function measured using MMSE
- Motor function measured using Motoricity Index
- Leaving the study early
- Adverse events
- Death

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Low risk | **Quote:** "treatment lasted up to 45 days (end point) and was given in the form of identical white capsules containing 20 mg of either fluoxetine or placebo, delivered in boxes coded by the central pharmacy of the University Hospital complex of Bordeaux" (p. 1829) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | **Quote:** "treatment lasted up to 45 days (end point) and was given in the form of identical white capsules containing 20 mg of either fluoxetine or placebo, delivered in boxes coded by the central pharmacy of the University Hospital complex of Bordeaux" (p. 1829) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** double-blind reported but who was blinded not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Quote:** "an intent-to-treat statistical analysis was conducted in which the last visit recorded was used as an end point" (p. 1830)<br>**Comment:** missing data were handled using last observation carried forward method |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |

**Yang 2002**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** paroxetine (SSRI)<br>**Control arm:** matched placebo |
| Participants | **Geographical location:** China |


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**Yang 2002** *(Continued)*

| | |
|---|---|
| | **Setting:** outpatient<br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** HDRS score > 7<br><br>**Total number randomised in this trial:** 121<br><br>**Number included in treatment group:** 64 (63% men, mean age 64 years, SD 3)<br>**Number included in control group:** 57 (56% men, mean age 63 years, SD 5)<br><br>**Total number included in final analysis:** 110<br><br>**Number included in treatment group for final analysis:** unclear<br><br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** paroxetine (SSRI) 20 mg daily<br>**Control:** matched placebo<br>**Duration:** 4 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression (50% reduction in scores from baseline to end of treatment) measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** blinding of outcome assessment not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | **Comment:** per protocol analysis reported only; 11/121 (9%) excluded from analysis |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |


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**Yang 2013**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** high-frequency rTMS + antidepressants<br>**Control arm:** sham rTMS + antidepressants |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** confirmed brain CT or MRI<br>**Inclusion criteria:** (1) 24-item HDRS score ≥ 8; (2) first stroke; (3) right-handedness; (4) clear consciousness; (5) able to express personal will<br>**Exclusion criteria:** (1) history of epilepsy, metal implant in the body; (2) history or family history of psychiatric illness<br>**Depression criteria:** 24-item HDRS score ≥ 8<br>**Total number randomised in this trial:** 38<br>**Number randomised to treatment group:** 19 (63% men; mean age 61, SD 8)<br>**Number randomised to control group:** 19 (52.6% men; mean age 60, SD 9)<br>**Total number included in final analysis:** 38<br>**Number included in treatment group for final analysis:** 19<br>**Number included in control group for final analysis:** 19 |
| Interventions | **Treatment:** high-frequency rTMS + antidepressants. Frequency: 10 Hz, intensity: 80% motor threshold, 1 stimulation lasts 4.9 seconds and stops for 20 seconds, total impulse number: 1960/d, 16 minutes per day, for 10 working days, location: left DLPFC<br>**Control:** sham rTMS + antidepressants. Keeping the coils at 90-degree angles with the scalp<br>**Duration:** 2 weeks<br>**Follow-up:** 4 weeks |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |


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**Yang 2013** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Yang 2014a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** high-frequency rTMS<br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** China<br>**Setting:** mixed<br>**Stroke criteria:** not reported<br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) 24-item HDRS score ≥ 8; (3) first stroke; (4) clear consciousness; (5) able to express personal will and to sign informed consent<br>**Exclusion criteria:** (1) history or family history of psychiatric illness; (2) unable to co-operate with the examination due to obvious aphasia or severe cognitive dysfunction; (3) history of epilepsy, metal implant in the body<br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression and 24-item HDRS score ≥ 8<br>**Total number randomised in this trial:** 56<br>**Number randomised to treatment group:** 37 (75.6% men; mean age 56.6, SD 13.6)<br>**Number randomised to control group:** 19** (73% men; mean age 53.3, SD 14.6)<br>**Total number included in final analysis:** 55<br>**Number included in treatment group for final analysis:** 37<br>**Number included in control group for final analysis:** 19** |


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**Yang 2014a** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** high-frequency rTMS. Frequency: 10 Hz, intensity: 90% motor threshold, 1 stimulation lasts 5 seconds and stops for 35 seconds, total impulse number: 1500, location: left DLPFC<br><br>**Control:** sham rTMS. With coils kept at 90-degree angles with the scalp and with coils contacting the scalp, participants could hear the click sounds<br><br>**Duration:** 2 weeks<br><br>**Follow-up:** 4 weeks |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Yang 2014b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** low-frequency rTMS<br><br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** China<br><br>**Setting:** mixed |


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**Yang 2014b** *(Continued)*

| | |
|---|---|
| | **Stroke criteria**: not reported<br><br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br><br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) 24-item HDRS score ≥ 8; (3) first stroke; (4) clear consciousness; (5) able to express personal will and to sign informed consent<br><br>**Exclusion criteria:** (1) history or family history of psychiatric illness; (2) unable to co-operate with the examination due to obvious aphasia or severe cognitive dysfunction; (3) history of epilepsy, metal implant in the body<br><br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression and 24-item HDRS score ≥ 8<br><br>**Total number randomised in this trial:** 55<br><br>**Number randomised to treatment group:** 37 (81% men; mean age 52.3, SD 11)<br><br>**Number randomised to control group:** 18** (73% men; mean age 53.3, SD 14.6)<br><br>**Total number included in final analysis:** 55<br><br>**Number included in treatment group for final analysis:** 37<br><br>**Number included in control group for final analysis:** 18** |
| Interventions | **Treatment:** low-frequency rTMS. Frequency: 1 Hz, intensity: 90% motor threshold, 1 stimulation lasts 10 seconds and stops for 2 seconds, total impulse number: 1000, location: left DLPFC<br><br>**Control:** sham rTMS. With coils kept at 90-degree angles with the scalp and with coils contacting the scalp, participants could hear the click sounds<br><br>**Duration:** 2 weeks<br><br>**Follow-up:** 4 weeks |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |


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**Yang 2014b** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Zhang 2013**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS + fluoxetine + stroke medications<br><br>**Control arm:** fluoxetine + stroke medications |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br><br>**Method of stroke diagnosis:** complying with diagnostic criteria for cerebral infarction and cerebral haemorrhage formulated by the Fourth National Conference on Cerebrovascular Diseases<br><br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) 17-item HDRS score ≥ 17; (3) no history of psychiatric illness and history of drug abuse or alcohol; (4) not taking any antipsychotic drugs 2 weeks before enrolment; (5) relatively stable clinical condition, able to clearly express feelings, no communication obstacle; (6) age 40 to 70 years, Han ethnic group, co-operative during treatment, able to complete all exams and to sign informed consent, educational level: junior high school or above<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression and 17-item HDRS score ≥ 17<br><br>**Total number randomised in this trial:** 82<br><br>**Number randomised to treatment group:** 41 (56% men; mean age 56.9, SD 5.8)<br><br>**Number randomised to control group:** 41 (53.6% men; mean age 57.7, SD 6.6)<br><br>**Total number included in final analysis:** 82<br><br>**Number included in treatment group for final analysis:** 41<br><br>**Number included in control group for final analysis:** 41 |
| Interventions | **Treatment:** rTMS + fluoxetine (20 mg/d) + stroke medications. Frequency: 10 Hz, intensity: 90% motor threshold, 1 stimulation lasts 4 seconds in 1 series, 20 series a day, 3 times a week, location: left DLPFC<br><br>**Control:** fluoxetine + stroke medications<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** none |


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**Zhang 2013** *(Continued)*

| | |
|---|---|
| Outcomes | **Primary outcome**<br>• Depression measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | **Comment:** random number table used for sequence generation |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

**Zhao 2004**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** psychoeducation<br>**Control arm:** usual care |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria**: not reported<br>**Method of stroke diagnosis:** diagnosis via CT or MRI (100%)<br>**Time since stroke:** not reported<br>**Inclusion criteria:** (1) cognitively competent; (2) no acute medical problems<br>**Exclusion criteria:** (1) serious mental problems; (2) low intelligence; (3) other serious neurological condition; (4) heart failure; (5) other acute disease |


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**Zhao 2004** *(Continued)*

| | |
|---|---|
| | **Depression criteria:** HDRS score > 17<br><br>**Total number randomised in this trial:** 70<br><br>**Number randomised to treatment group:** 35 (57% men, mean age 65 years, SD 13)<br>**Number randomised to control group:** 35 (51% men, mean age 61 years, SD 14)<br><br>**Total number included in final analysis:** 70<br><br>**Number included in treatment group for final analysis:** 35<br><br>**Number included in control group for final analysis:** 35 |
| Interventions | **Treatment:** psychoeducation, daily, less than 30 minutes<br><br>**Administered by:** special personnel who received 2 weeks training before the trial started<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** unclear; no formal evaluation of the quality or content of therapy provided<br><br>**Control:** usual care<br><br>**Duration:** 4 weeks<br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression (reduction in scores from baseline to end of treatment) measured using HDRS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not stated |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | **Comment:** single-blind reported; participants not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | **Comment:** outcome assessment blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported (complete follow-up of all randomised participants) |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographic characteristics between groups |


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**Zheng 2016**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** intra-low frequency (ILF)-TMS + cerebrovascular disease routine care + early rehabilitation<br><br>**Control arm:** cerebrovascular disease routine care + early rehabilitation |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Number of participants:** 82<br><br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br><br>**Method of stroke diagnosis:** complying with diagnostic criteria for cerebral infarction and cerebral haemorrhage formulated by the Fourth National Conference on Cerebrovascular Diseases<br><br>**Inclusion criteria:** (1) meeting diagnostic criteria of the CCMD-3 for depression; (2) stable vital signs, ability to understand and perform rehabilitation<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) dementia; (3) severe physical illness; (4) history of epilepsy<br><br>**Depression criteria:** meeting diagnostic criteria of the CCMD-3 for depression<br><br>**Total number randomised in this trial:** 82<br><br>**Number randomised to treatment group:** 41 (56% men; mean age 63.8, SD 8.5)<br><br>**Number randomised to control group:** 41 (60% men; mean age 64.3, SD 6.9)<br><br>**Total number included in final analysis:** 82<br><br>**Number included in treatment group for final analysis:** 41<br><br>**Number included in control group for final analysis:** 42 |
| Interventions | **Treatment:** intra-low frequency (ILF)-TMS + cerebrovascular disease routine care + early rehabilitation. Frequency: < 0.2 Hz, 20 minutes per treatment, and 1 treatment per day, at least 5 times a week, lasting for 2 successive courses<br><br>**Control:** cerebrovascular disease routine care + early rehabilitation<br><br>**Duration:** 4 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Impairment measured using SSS |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|


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**Zheng 2016** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | **Comment:** method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | **Comment:** method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of participants and personnel not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | **Comment:** information about blinding of outcome assessors not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | **Comment:** ITT analysis reported; no missing data |
| Selective reporting (reporting bias) | Unclear risk | **Comment:** all pre-specified outcomes reported; no trial protocol available to compare with the publication |
| Other bias | Low risk | **Comment:** no differences in baseline demographics between groups |

** Results for control group halved.
^ Results for attention control and control group pooled.
ABI: acquired brain injury.
ADL: activities of daily living.
AE: adverse event.
AHI: Authentic Happiness Inventory.
BDI: Beck Depression Inventory.
BI: Barthel Index.
BZDs: benzodiazepines.
CBT: cognitive-behavioural therapy.
CCMD-2-R: Chinese Classification of Mental Disorders, Second Edition, Revised.
CCMD-3: Chinese Classification of Mental Disorders, Third Edition.
CGI: Clinical Global Impression Scale.
CIPI: constructive integrative psychosocial intervention.
CNS: central nervous system.
CSI: Caregiver Strain Index.
CSS: Chinese Stroke Scale.
CT: computed tomography.
DASS-21: Depression Anxiety Stress Scales - 21 items.
DLPFC: dorsolateral pre-frontal cortex.
DSM: Diagnostic and Statistical Manual.
EADL: extended activities of daily living.
EFT: ecosystem focused therapy.
ESD: Education on Stroke and Depression.
FAC: Functional Ambulatory Category.
FIM: Functional Independence Measure.
GCS: Glasgow Coma Scale.
GDS: Geriatric Depression Scale.
GHQ-28: 28-item General Health Questionnaire.
HADS: Hospital Anxiety Depression Scale.
HARS: Hamilton Anxiety Rating Scale.
HDRS-24: 24-item Hamilton Depression Rating Scale.
HDRS-17: 17-item Hamilton Depression Rating Scale.
HRQoL: health-related quality of life.


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Hz: Hertz.
ICD: International Classification of Diseases.
ILF: intra-low frequency.
ITT: intention to treat.
LTF: loss to follow-up.
LOCF: last observation carried forward.
MADRS: Montgomery Asberg Depression Rating Scale.
MBC: Modified Brunnstrom Classification.
MBI: Modified Barthel Index.
MI: motivational interviewing.
MMSE: Mini Mental State Examination.
MPAI-4: Mayo-Portland Adaptability Inventory-4.
MRI: magnetic resonance imaging.
NIHSS: National Institute of Health Stroke Scale.
NRI: norepinephrine reuptake inhibitor.
P300: the P300 is a wave that represents a positive deflection in the human event-related potential. It is most commonly elicited when a patient detects an occasional "target" stimulus in a regular train of standard stimuli.
PHQ-9: 9-item Patient Health Questionnaire.
PSE: Present State Examination.
QoL: quality of life.
rTMS: repetitive transcranial magnetic stimulation.
SAD-Q: Stroke Aphasia Depression Questionnaire.
SAH: subarachnoid haemorrhage.
SAQoL: Stroke Aphasia Quality of Life Scale.
SCAN: Schedules for Clinical Assessment in Neuropsychiatry.
SD: standard deviation.
SDS: Severity of Dependence Scale.
SE: standard error.
SNRI: selective norepinephrine reuptake inhibitor.
SSRI: selective serotonin reuptake inhibitor.
SSS: Scandinavian Stroke Scale.
TCA: tricyclic antidepressant.
TMS: transcranial magnetic stimulation.
VAMS: Visual Analogue Mood Scale.
VAS: visual analogue scale (100 mm).
WDI: Wakefield Depression Inventory.
WHO: World Health Organization.
WHODAS- II: World Health Organization Disability Assessment Schedule.
ZDS: Zung Depression Scale.

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

| Study | Reason for exclusion |
|---|---|
| Aben 2014 | Depression not the primary outcome of this study |
| Agnoli 1985 | Inability to isolate stroke patients |
| Bai 2017 | Depression not the primary outcome of this study |
| Bramanti 1989 | Data not available for depressed participants only |
| Casella 1960 | Depression not the primary outcome of this study |
| Chang 2011 | Data not available for depressed participants only |
| Cheng 2016 | Depression not the primary outcome of this study |
| Choi-Kwon 2006 | Data not available for depressed participants only |


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| Study | Reason for exclusion |
|---|---|
| Chollet 2011 | Depression not the primary outcome of this study |
| Clark 2003 | Data not available for depressed participants only |
| Delbari 2011 | Data not available for depressed participants only |
| Downes 1995 | Data not available for depressed participants only |
| Evans 1997 | Participants were acute geriatric medical inpatients with depression. We were unable to isolate any chronic stroke patients. No acute stroke patients were included in the sample |
| Finkenzeller 2006 | Depression assessments not available at a consistent time point |
| Hadidi 2014 | Data not available for depressed participants only |
| Hu 2003 | Depression not the primary outcome of this study |
| ISRCTN88489864 | Depression not the primary outcome of this study |
| Jiang 2004 | Depression not the primary outcome of this study |
| Jorge 2004 | Data not available for depressed participants only |
| Jorge 2008 | Data not available for depressed participants only |
| Kim 2010a | Data not available for depressed participants only |
| Kim 2010b | Data not available for depressed participants only |
| Kim 2017 | Data not available for depressed participants only |
| Kim 2017a | Data not available for depressed participants only |
| Kootker 2012 | Data not available in the format suitable for this review |
| Laska 2005 | Depression not an outcome of this study |
| Leijon 1989 | Depression not an outcome of this study |
| Lobjanidze 2010 | Depression not the primary outcome of this study |
| Mauri 1988 | Data not available in a format suitable for this review |
| Meara 1998 | Data not available for depressed participants only |
| Narushima 2007 | Depression not the primary outcome of this study |
| Ohtomo 1985 | Data not available for depressed participants only |
| Ostwald 2014 | Data not available for depressed participants only |
| Otomo 1986 | Participants not depressed at entry into the study |
| Raffaele 1996 | Data not available for depressed participants only |


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| Study | Reason for exclusion |
|---|---|
| Rich 2016 | Depression not the primary outcome of this study |
| Robinson 2000 | Data not available for depressed participants only |
| Robinson 2017 | Depression not the primary outcome of this study |
| Rudberg 2017 | Depression not the primary outcome of this study |
| Sieger 2018 | Depression not the primary outcome of this study |
| Sivenius 2001 | Depression not the primary outcome of this study |
| Su 2004a | Depression not the primary outcome of this study |
| Sun 2000 | Data not available for depressed participants only |
| Szepfalusi 2017 | Depression not the primary outcome of this study |
| Valiengo 2017 | Data not available for depressed participants only |
| Visser 2015 | Depression not the primary outcome of this study |
| Walker-Batson 1995 | Depression not the primary outcome of this study |
| Wang 2009 | Depression not the primary outcome of this study |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

### Chen 2002a

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** paroxetine (SSRI)<br><br>**Control arm:** placebo |
| Participants | **Geographical location:** China<br>**Setting:** unclear<br>**Number of participants:** 36<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) cognitive impairment (MMSE < 24); (2) depression deterioration (HDRS > 24); (3) suicidal mood; (4) drug intolerability<br><br>**Depression criteria:** unclear<br><br>**Total number randomised in this trial:** 36<br><br>**Number randomised to treatment group:** 24<br><br>**Number randomised to control group:** 12** |


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**Chen 2002a** *(Continued)*

| | |
|---|---|
| | **Total number included in final analysis:** 34<br>**Number included in treatment group for final analysis:** 24<br>**Number included in control group for final analysis:** 10** |
| Interventions | **Treatment:** paroxetine (SSRI) 200 mg once daily<br>**Control:** placebo (guvitamine) 10 mg 3 × daily<br>**Duration:** 8 weeks<br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>**Secondary outcomes**<br>• Disability measured using BI<br>• Impairment measured using CSS |
| Notes | Unable to obtain information on the primary outcome: whether depression or functional recovery |

**Chen 2002b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** doxepin<br>**Control arm:** placebo |
| Participants | **Geographical location:** China<br>**Setting:** unclear<br>**Number of participants:** 36<br>**Stroke criteria:** unclear<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** (1) cognitive impairment (MMSE < 24); (2) depression deterioration (HDRS > 24); (3) suicidal mood; (4) drug intolerability<br>**Depression criteria:** unclear<br>**Total numbers randomised in this trial:** 36<br>**Numbers randomised to treatment group:** 24<br>**Numbers randomised to control group:** 12**<br>**Total numbers included in final analysis:** 26<br>**Numbers included in treatment group for final analysis:** 16<br>**Numbers included in control group for final analysis:** 10** |
| Interventions | **Treatment:** doxepin 25 mg 3 × daily |


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**Chen 2002b** *(Continued)*

| | |
|---|---|
| | **Control:** placebo (guvitamine) 10 mg 3 × daily<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcome**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Disability measured using BI<br>• Impairment measured using CSS |
| Notes | Unable to obtain information on the primary outcome: whether depression or functional recovery |

**Ding 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Treatment arm:** paroxetine (SSRI) + psychotherapy + education<br><br>**Control arm:** paroxetine (SSRI) |
| Participants | **Geographical location:** China<br>**Setting:** outpatient<br><br>**Stroke criteria:** ischaemic and haemorrhagic stroke<br><br>**Method of stroke diagnosis:** clinical diagnosis with imaging consistent with stroke using Oxford Community Stroke Project classification and structural brain CT classification (by anatomical location)<br><br>**Time since stroke:** 2 to 6 months<br><br>**Inclusion criteria:** (1) meeting depression diagnostic criteria of the CCMD-3 and 17-item HDRS score > 17)<br><br>**Exclusion criteria:** (1) bipolar disorders; (2) drug dependence or abuse<br><br>**Depression criteria:** psychiatric interview; meeting depression diagnostic criteria of the CCMD-3; 17-item HDRS score > 17; HARS score > 7; clinical impression<br><br>**Total number randomised in this trial:** 68<br><br>**Number randomised to treatment group:** 34 (56% men; mean age 61.3 years, SD 9.3)<br><br>**Number randomised to control group:** 34 (47% men; mean age 60.5 years, SD 10.4)<br><br>**Total number included in final analysis:** 68<br><br>**Number included in treatment group for final analysis:** 34 (56% men; mean age 61.3 years, SD 9.3)<br><br>**Number included in control group for final analysis:** 34 (47% men; mean age 60.5 years, SD 10.4) |
| Interventions | **Treatment:** combination of paroxetine (SSRI, variable dose, started from 10 mg/d, titrated up to 20 to 30 mg/d) + psychotherapy: combination of cognitive therapy targeted at beliefs about stroke de- |


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**Ding 2005** *(Continued)*

| | |
|---|---|
| | pression; behavioural therapy targeted at attitudes in practice and education. Psychotherapy was delivered in 40 to 60-minute sessions, 2 to 3 sessions a week<br><br>**Administered by:** a professional physician; training in psychotherapy unclear<br><br>**Supervision of therapists:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** paroxetine (SSRI, variable dose, started from 10 mg/d, titrated up to 20 to 30 mg/d)<br><br>**Duration:** 8 weeks<br><br>**Follow-up:** 4 months |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Anxiety measured using HARS<br>• Activities of daily living measured using BI<br>• Symptoms measured using Treatment Emergent Symptom Scale |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Evans 1985**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** telephone counselling<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** USA<br><br>**Setting:** outpatient<br><br>**Stroke criteria:** unclear (also includes people with spinal cord injury, CNS disease, and 'other')<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) patients discharged from rehabilitation centre; (2) housebound; (3) able to hear; (4) ordinary speech; (5) sufficient cognitive ability to engage in meaningful conversation<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** score taken from the Life Satisfaction Index (LSI); unclear how scored<br><br>**Total number randomised in this trial:** 38<br><br>**Number randomised to treatment group:** 19 (95% men, mean age 54.8 years, SD 11.9 years); 4 with stroke<br><br>**Number randomised to control group:** 19 (95% men, mean age 54.8 years, SD 10.2 years); 5 with stroke<br><br>**Total number included in final analysis:** unclear |


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**Evans 1985** *(Continued)*

| | |
|---|---|
| | **Number included in treatment group for final analysis:** unclear<br><br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** 8-weekly hour-long counselling sessions by phone with groups of 4 patients. Formulation of behaviorally specific goals encouraged and developed with each patient, and discussion directed at finding ways to meet those goals<br><br>**Administered by:** an experienced counsellor<br><br>**Supervision:** not reported<br><br>**Control:** usual care (no contact)<br><br>**Duration:** not reported<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcome**<br><br>• Depression - unclear what measure was used |
| Notes | Unable to obtain any more information on this trial or series of trials despite multiple attempts since 2003 |

**Finkenzeller 2009**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** sertraline (SSRI) + psychological therapy<br><br>**Control arm:** sertraline (SSRI) |
| Participants | **Geographical location:** Germany<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** all subtypes<br><br>**Method of stroke diagnosis:** unclear<br><br>**Time since stroke:** < 3 months<br><br>**Inclusion criteria:** (1) onset of stroke no longer than 3 months<br><br>**Exclusion criteria:** (1) previous or current psychiatric disorder like substance abuse, borderline or antisocial personality disorder, or other prominent Axis I disorder; (2) with previous depressive disorder, only if participants were still treated with antidepressive medication for this matter; (3) stronger cognitive impairment (e.g. dementia, aphasia, delirium) (no defined criteria or cut-off)<br><br>**Depression criteria:** HADS > 7 on the subscale Depression, HDRS score > 13<br><br>**Total number randomised in this trial:** 21<br><br>**Number randomised to treatment group:** 9 (39% men, mean age 64.7, SD 11.1)<br><br>**Number randomised to control group:** 12 (50% men, mean age 71.7, SD 7.1)<br><br>**Total number included in final analysis:** 21 |


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**Finkenzeller 2009** *(Continued)*

| | |
|---|---|
| | **Number included in treatment group for final analysis:** 9 (39% men, mean age 64.7, SD 11.1)<br>**Number included in control group for final analysis:** 12 (50% men, mean age 71.7, SD 7.1) |
| Interventions | **Treatment:** sertraline (SSRI) 50 mg/d + psychological therapy (twice a week)<br>**Administered by:** not reported<br>**Supervision:** not reported<br>**Intervention fidelity:** not reported<br>**Control:** sertraline (SSRI)<br>**Duration:** 4 to 8 weeks<br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression (response > 50% reduction in initial score) measured using HDRS<br>• Depression (remission) measured using HDRS (< 8) |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Hanspal 2007**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** sertraline (SSRI)<br>**Control arm:** placebo |
| Participants | **Geographical location:** UK<br>**Setting:** unclear<br>**Stroke criteria:** unclear (also includes people with non-vascular events such as trauma, hypoxia, or encephalitis)<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** not reported<br>**Depression criteria:** unclear<br>**Total number randomised in this trial:** unclear<br>**Number randomised to treatment group:** unclear<br>**Number randomised to control group:** unclear<br>**Total number included in final analysis:** unclear<br>**Number included in treatment group for final analysis:** unclear<br>**Number included in control group for final analysis:** unclear |


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**Hanspal 2007** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** sertraline (SSRI)<br>**Control:** placebo<br>**Duration:** not reported<br>**Follow-up:** not reported |
| Outcomes | **Primary outcome**<br>• Depression: unclear what measure was used |
| Notes | Unable to obtain any more information on this trial despite multiple attempts since 2007 |

**He 2003**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Treatment arm:** amitriptyline (TCA) + psychological intervention + routine drugs for cerebrovascular disease<br>**Control arm:** amitriptyline (TCA) + routine drugs for cerebrovascular disease |
| Participants | **Geographical location:** China<br>**Setting:** unclear<br>**Stroke criteria:** cerebral infarction and haemorrhage<br>**Method of stroke diagnosis:** stroke diagnosed according to the standards of National Fourth Cerebral Vascular Disease Meeting of Chinese Medical Association in 1995<br>**Inclusion criteria:** (1) score > 8 in the CCMD-2-R<br>**Exclusion criteria:** (1) history of mental disorder; (2) patients with coma, anepia, intelligence disorder; (3) patients with severe disease of heart, liver, and lung<br>**Depression criteria:** score > 8 in the CCMD-2-R<br>**Total number randomised in this trial:** 67<br>**Number randomised to treatment group:** 35 (54.3% men, mean 64 years, SD 9)<br>**Number randomised to control group:** 32 (percentage of men and mean age not reported for this group)<br>**Total number included in final analysis:** unclear<br>**Number included in treatment group for final analysis:** unclear<br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** amitriptyline (TCA + psychological intervention + routine drugs for cerebrovascular disease). Psychological intervention included (1) treatment of cognitive behaviour; (2) supportive psychological treatment; (3) education about hypertension, coronary heart disease, and diabetes; (4) education about psychological hygiene<br>**Administered by:** not reported<br>**Supervision:** not reported |


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**He 2003** *(Continued)*

| | |
|---|---|
| | **Intervention fidelity:** not reported<br><br>**Control:** amitriptyline (TCA) + routine drugs for cerebrovascular disease<br><br>**Duration:** 6 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Activities of daily living (unclear what measure was used) |
| Notes | Unable to obtain information on the intervention of this trial |

**He 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** paroxetine (SSRI)<br><br>**Control arm:** psychotherapy + paroxetine (SSRI) |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic stroke and cerebral haemorrhage<br><br>**Method of stroke diagnosis:** first-ever stroke with a diagnosis consistent with diagnostic criteria for cerebral infarct formulated by the Fourth National Conference on Cerebrovascular Disease and confirmation by brain CT or MRI<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) first-ever stroke; (2) meeting organic depressive disorder/organic anxiety disorder diagnostic criteria of ICD-10; (3) 17-item HDRS score ≥ 17; HARS score ≥ 14<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) taking antidepressants and neuroleptics in the previous 3 months; (3) aphasia; (4) severe cognitive impairment; (5) allergy to paroxetine; (6) suicidal behaviour; (7) in a coma<br><br>**Depression criteria:** meeting organic depressive disorder/organic anxiety disorder diagnostic criteria of ICD-10 and 17-item HDRS score ≥ 17; HARS score ≥ 14<br><br>**Total number randomised in this trial:** 54<br><br>**Number randomised to treatment group:** 27 (52% men; mean age 64, SD 5.3)<br><br>**Number randomised to control group:** 27 (52% men; mean age 62.4, SD 6.1)<br><br>**Total number included in final analysis:** 54<br><br>**Number included in treatment group for final analysis:** 27<br><br>**Number included in control group for final analysis:** 27 |
| Interventions | **Treatment:** combined psychotherapy (early supportive psychotherapy (1 × 30 minutes session/week) + paroxetine (SSRI) 20 mg/d<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported |


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**He 2005** *(Continued)*

| | |
|---|---|
| | **Intervention fidelity:** not reported<br><br>**Control:** paroxetine (SSRI) 20 mg/d<br><br>**Duration:** 6 weeks<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Anxiety measured by HARS<br><br>**Secondary outcomes**<br><br>• Symptoms measured using Treatment Emergent Symptom Scale<br>• Disability measured using BI<br>• Impairment measured using SSS |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Huang 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** venlafaxine (SNRI) + cognitive therapy<br><br>**Control arm:** venlafaxine (SNRI) |
| Participants | **Geographical location:** China<br>**Setting:** mixed<br>**Stroke criteria:** ischaemic stroke only<br><br>**Method of stroke diagnosis:** first-ever stroke with diagnosis consistent with diagnostic criteria for cerebral infarct formulated by the Fourth National Conference on Cerebrovascular Disease and confirmation by brain CT or MRI<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) first-ever stroke; (2) depression developed in the acute stage of cerebral infarct; (3) HDRS score ≥ 18<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) dementia; (3) aphasia; (4) consciousness disturbance; (5) apraxia; (6) other organic disease; (7) systematic disease; (8) depression developed in the acute stage of cerebral infarct<br><br>**Depression criteria:** HDRS score ≥ 18; depression developed in the acute stage of cerebral infarct<br><br>**Total number randomised in this trial:** 82<br><br>**Number randomised to treatment group:** 41 (% men not reported, mean age 62.2 years, SD 8.3)<br><br>**Number randomised to control group:** 41 (% men not reported, mean age 61.8 years, SD 8.7)<br><br>**Total number included in final analysis:** 80<br><br>**Number included in treatment group for final analysis:** 40 (63% men, mean age not reported)<br><br>**Number included in control group for final analysis:** 40 (61% men, mean age not reported) |


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**Huang 2005** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** venlafaxine (SNRI) 121.56 mg/d + combined cognitive therapy (more than 1 hour every session, 1 session/week initially, 1 session fortnightly 1 month later, and 1 to 2 sessions/month 2 months later)<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** venlafaxine (SNRI) 121.56 mg/d<br><br>**Duration:** 3 months<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Symptoms measured using Treatment Emergent Symptom Scale |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Katz 1998**

| | |
|---|---|
| Methods | **Study design:** unclear<br><br>**Number of arms:** 4<br><br>**Experimental arm 1:** group psychotherapy<br><br>**Experimental arm 2:** behavioral therapy<br><br>**Experimental arm 3:** combined antidepressant and individual psychotherapy plus group psychotherapy<br><br>**Control arm:** unclear |
| Participants | **Geographical location:** unclear<br><br>**Setting:** unclear<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** unclear<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** unclear<br><br>**Total number randomised in this trial:** unclear<br><br>**Number randomised to treatment group:** unclear<br><br>**Number randomised to control group:** unclear |


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**Katz 1998** *(Continued)*

| | |
|---|---|
| | **Total number included in final analysis:** unclear<br>**Number included in treatment group for final analysis:** unclear<br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment 1:** group psychotherapy<br>**Treatment 2:** behavioural therapy<br>**Treatment 3:** combined antidepressant and individual psychotherapy plus group psychotherapy<br>**Control:** unclear<br>**Duration:** not reported<br>**Follow-up:** not reported |
| Outcomes | **Primary outcome**<br>• Depression - unclear what measure was used |
| Notes | Unable to obtain any more information on this trial or series of trials despite multiple attempts since 2002 |

**Latow 1983**

| | |
|---|---|
| Methods | **Study design:** unclear<br>**Number of arms:** unclear<br>**Experimental arm:** psychotherapy<br>**Control arm:** unclear |
| Participants | **Geographical location:** unclear<br>**Setting:** unclear<br>**Number of participants:** unclear<br>**Stroke criteria:** unclear<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** not reported<br>**Depression criteria:** unclear<br>**Total number randomised in this trial:** unclear<br>**Number randomised to treatment group:** unclear<br>**Number randomised to control group:** unclear<br>**Total number included in final analysis:** unclear<br>**Number included in treatment group for final analysis:** unclear<br>**Number included in control group for final analysis:** unclear |


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**Latow 1983** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** psychotherapy<br>**Control:** unclear<br>**Duration:** unclear<br>**Follow-up:** unclear |
| Outcomes | **Primary outcome**<br>• Depression - unclear what measure was used |
| Notes | Unable to obtain a copy of this article, which also may be a book |

**Lee 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS<br>**Control arm:** sham stimulation |
| Participants | **Geographical location:** Republic of Korea<br>**Setting:** not reported<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** radiological diagnosis of location of infarct is given, but it is unclear whether this was used to make the diagnosis<br>**Inclusion criteria:** (1) patients who did not respond to conventional antidepressant medication (paroxetine 20 mg/d); (2) Rancho Los Amogos cognitive function scale more than VIIa<br>**Exclusion criteria:** (1) history of psychiatric illness; (2) aphasia; (3) arrhythmia; (4) left pre-frontal cortical lesion; (5) seizure or internal metallic device<br>**Depression criteria:** BDI > 17<br>**Total number randomised in this trial:** 20<br>**Number randomised to treatment group:** 10 (70% men, mean age 67.8, SD 2.3)<br>**Number randomised to control group:** 10 (60% men, mean age 66.3, SD 3.0)<br>**Total number included in final analysis:** unclear<br>**Number included in treatment group for final analysis:** unclear<br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** rTMS 10 Hz at an intensity of 110% for 1 second<br>**Administered by:** not reported<br>**Control:** sham stimulation<br>**Frequency:** 10 trains separated by 60 seconds<br>**Duration:** for 10 days during a 2-week period |


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**Lee 2005** *(Continued)*

| | |
|---|---|
| | **Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Depression measured using BDI<br>**Secondary outcomes**<br>• Cognitive function measured using MMSE |
| Notes | Unable to obtain any more information on this trial despite multiple attempts since 2008 |

**Liu 2010**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS + routine care + physical factors treatment + acupuncture + psychotherapy<br>**Control arm:** sham rTMS + routine care + physical factors treatment + acupuncture + psychotherapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** ischaemic stroke<br>**Method of stroke diagnosis:** clinical diagnosis plus confirmation by imaging that a relevant lesion needed to be visible<br>**Inclusion criteria:** (1) no dementia; (2) no aphasia; (3) clear consciousness; (4) age < 75 years<br>**Exclusion criteria:** (1) cerebral haemorrhage; (2) history of epilepsy; (3) metal implant in the body; (4) other serious physical illness; (5) history of psychiatric illness or family history<br>**Depression criteria:** meeting diagnostic criteria of ICD-10 for depression and 24-item HDRS score > 20<br>**Total number randomised in this trial:** 60<br>**Number randomised to treatment group:** 30 (36% men; mean age 59, SD 9)<br>**Number randomised to control group:** 30 (30% men; mean age 58, SD 11)<br>**Total number included in final analysis:** 60<br>**Number included in treatment group for final analysis:** 30<br>**Number included in control group for final analysis:** 30 |
| Interventions | **Treatment:** rTMS + routine care (medications (sertraline or citalopram), physical factors treatment (musical therapy, high-voltage static current therapy), Chinese medicine (acupuncture), and psychotherapy (patient-centred therapy, cognitive therapy, behaviour therapy)). Frequency: 10 to 15 Hz, intensity: 90% motor threshold, 1 stimulation lasting 1 second and stop for 10 seconds, total 1200 stimulations per day, for 10 days, location: left DLPFC<br>**Control:** sham rTMS + routine care (medications (sertraline or citalopram), physical factors treatment (musical therapy, high-voltage static current therapy), Chinese medicine (acupuncture), and |


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**Liu 2010** *(Continued)*

| | |
|---|---|
| | psychotherapy (patient-centred therapy, cognitive therapy, behaviour therapy)). Keeping the coils at 90-degree angle with the scalp, keeping the coils at a distance of 8 cm from treatment area<br><br>**Duration:** 10 days<br><br>**Follow-up:** 40 days |
| Outcomes | **Primary outcome**<br><br>• Depression measured using HDRS |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Pearson 2005**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** nurse-led education intervention<br><br>**Control arm:** unclear |
| Participants | **Geographical location:** unclear<br><br>**Setting:** outpatient<br><br>**Number of participants:** 41<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** unclear<br><br>**Total number randomised in this trial:** 41<br><br>**Number randomised to treatment group:** 20<br><br>**Number randomised to control group:** 21<br><br>**Total number included in final analysis:** unclear<br><br>**Number included in treatment group for final analysis:** unclear<br><br>**Number included in control group for final analysis:** unclear |
| Interventions | **Treatment:** Orem's self-care model of nursing, Knowles' principles of adult learning, nurse-led educational intervention<br><br>**Control:** unclear<br><br>**Duration:** 16 hours<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcome** |


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**Pearson 2005** *(Continued)*

| | |
|---|---|
| | • Depression measured using BDI |
| Notes | Able to locate only conference abstract |

**Razazian 2016**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** fluoxetine (SSRI)<br><br>**Control arm:** placebo |
| Participants | **Geographical location:** Iran<br>**Setting:** inpatient<br>**Stroke criteria:** acute ischaemic stroke<br><br>**Method of stroke diagnosis:** documented with CT scan<br><br>**Time since stroke:** not reported<br><br>**Inclusion criteria:** (1) acute ischaemic stroke (documented with CT scan) that leads monoparesis, hemiparesis, or hemiplegia; (2) not in a comatose state and stable<br><br>**Exclusion criteria:** (1) death due to any cause during assessment; (2) pregnancy; (3) poor compliance of drugs and physiotherapy; (4) miscarriage returning of patient for further exams and assessments; (5) any drug complication during assessment (prospected or not); (6) any metabolic disease (liver, renal, cardiac impairment, and hyperthyroidism); (7) ischaemic stroke in the territory of anterior cerebral artery (ACA) or posterior cerebral artery (PCA), using any interfering drugs with fluoxetine (such as cyproheptadine, selegiline)<br><br>**Depression criteria:** none<br><br>**Total number randomised in this trial:** 172<br><br>**Number randomised to treatment group:** 86 (50.6% men; mean age 63.2, SD 11.4)<br><br>**Number randomised to control group:** 86 (41.3% men; mean age 64.6, SD 11.9)<br><br>**Total number included in final analysis:** 150<br><br>**Number included in treatment group for final analysis:** 75<br><br>**Number included in control group for final analysis:** 75 |
| Interventions | **Treatment:** fluoxetine (SSRI) 20 mg/d<br><br>**Control:** placebo<br><br>**Duration:** 45 days<br><br>**Follow-up:** 90 days |
| Outcomes | **Primary outcomes**<br><br>• Motor impairment<br>• Depression measured using ZDS<br>• Disability measured using BI |


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**Razazian 2016** *(Continued)*

| | |
|---|---|
| Notes | Unable to obtain information on the primary outcome: whether depression or functional recovery |

**Tang 2002**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** paroxetine (SSRI) + cognitive therapy (frequency unknown)<br><br>**Control arm:** paroxetine (SSRI) |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Second National Symposium on Cerebrovascular Disease and confirmation by brain CT or MRI<br><br>**Time since stroke:** 2 weeks ago<br><br>**Inclusion criteria:** (1) no history of aphasia or agnosia; (2) clear consciousness; (3) stroke onset at least 2 weeks ago<br><br>**Exclusion criteria:** (1) history of psychiatric illness; (2) organic or reactive depression; (3) comorbid with other severe psychiatric symptoms, or family history<br><br>**Depression criteria:** psychiatric interview to confirm diagnosis meets diagnostic criteria of CCMD-2-R; ZDS score ≥ 50<br><br>**Total number randomised in this trial:** 41<br><br>**Number randomised to treatment group:** 20 (60% men; mean age 57.5, SD 5.2)<br><br>**Number randomised to control group:** 21 (57% men; mean age 56.3, SD 5.7)<br><br>**Total number included in final analysis:** 41<br><br>**Number included in treatment group for final analysis:** 20<br><br>**Number included in control group for final analysis:** 21 |
| Interventions | **Treatment:** combined paroxetine (SSRI) 20 mg/d in the morning and cognitive therapy (frequency unknown). Cognitive therapy entailed guiding patients to apply cognitive remediation for negative thoughts; recognise situations causing depression; re-establish healthy ideas and attitudes; establish family co-operation<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** paroxetine (SSRI) 20 mg/d in the morning<br><br>**Duration:** 1 month<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using ZDS |


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**Tang 2002** *(Continued)*

| | |
|---|---|
| | **Secondary outcomes**<br>• Cognitive functioning measured using MMSE<br>• Evaluation of clinical status, stratifying clinical status as recovered (disappearance of symptoms, insight recovery, social function recovery), obviously improved (most symptoms disappear, insight partial recovery), improved (only slightly improved), not efficacious (no any improvement and even worse) |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Wang 2015**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rTMS + conventional drugs, rehabilitation training, and psychological counselling therapy<br>**Control arm:** conventional drugs, rehabilitation training, and psychological counselling therapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** not reported<br>**Method of stroke diagnosis:** clinical criteria only<br>**Inclusion criteria:** (1) meeting diagnostic criteria of ICD for organic depression; (2) 17-item HDRS score ≥ 8; (3) over 65 years of age<br>**Exclusion criteria:** not reported<br>**Depression criteria:** meeting diagnostic criteria of ICD for organic depression and 17-item HDRS score ≥ 8<br>**Total number randomised in this trial:** 150<br>**Number randomised to treatment group:** 75 (56% men; mean age 56.7, SD 7.2)<br>**Number randomised to control group:** 75 (53% men; mean age 57.9, SD 6.8)<br>**Total number included in final analysis:** 150<br>**Number included in treatment group for final analysis:** 75<br>**Number included in control group for final analysis:** 75 |
| Interventions | **Treatment:** rTMS + conventional drugs, rehabilitation training, and psychological counselling therapy. Frequency: 10 Hz, intensity: 60% motor threshold, 1 stimulation lasts 4 seconds and stops for 56 seconds, 30 stimulations for 1 series, 5 series a week, for successive 12 weeks, location: left DLF-PC<br>**Control:** conventional drugs, rehabilitation training, and psychological counselling therapy<br>**Duration:** 12 weeks<br>**Follow-up:** none |
| Outcomes | **Primary outcomes** |


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**Wang 2015** *(Continued)*

- Depression measured using HDRS
- Disability measured using BI

| | |
|---|---|
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Yan 2010a**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** high-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br><br>**Control arm:** sham rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** not reported<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995 and confirmation by brain CT or MRI stated<br><br>**Time since stroke:** < 6 months<br><br>**Inclusion criteria:** (1) right-handedness; (2) disease course < 6 months; (3) can sign informed consent<br><br>**Exclusion criteria:** (1) history of psychiatric illness or family history; (2) aphasia; (3) severe dementia; (4) severe physical illness, consciousness disturbance, or deafness, which influences the expression of depressed mood; (4) psychoactive or non-addiction-producing substance-induced depression; (5) various reasons to refuse trial or difficulty in finishing trial<br><br>**Depression criteria:** depression diagnosed according to CCMD-3<br><br>**Total number randomised in this trial:** 20<br><br>**Number randomised to treatment group:** 10 (50% men; mean age 68.65, SD 7.62)<br><br>**Number randomised to control group:** 10** (55% men; mean age 68.70, SD 8.94)<br><br>**Total number included in final analysis:** 20<br><br>**Number included in treatment group for final analysis:** 10<br><br>**Number included in control group for final analysis:** 10** |
| Interventions | **Treatment:** high-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy. High rTMS frequency: 10 Hz; intensity: 110% motor threshold; location: left DLPFC; 1 sequence included continuous stimulations for 30 minutes, frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Control:** sham rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 twice a day + psychotherapy. Sham rTMS 0 Hz; intensity: 0; location: left or right DLPFC; 1 sequence included continuous stimulations for 30 minutes, frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Duration:** 7 days |


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**Yan 2010a** *(Continued)*

| | |
|---|---|
| | **Follow-up:** none |
| Outcomes | **Primary outcomes**<br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br>**Secondary outcomes**<br>• Adverse events<br>• Leaving the trial early<br>• Death |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Yan 2010b**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** low-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br>**Control arm:** sham rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** not reported<br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995 and confirmation by brain CT or MRI stated<br>**Time since stroke:** < 6 months<br>**Inclusion criteria:** (1) right-handedness; (2) disease course < 6 months; (3) can sign informed consent<br>**Exclusion criteria:** (1) history of psychiatric illness or family history; (2) aphasia; (3) severe dementia; (4) severe physical illness, consciousness disturbance, or deafness, which influences the expression of depressed mood; (4) psychoactive or non-addiction-producing substance-induced depression; (5) various reasons to refuse trial or difficulty in finishing trial<br>**Depression criteria:** depression diagnosed according to the CCMD-3<br>**Total number randomised in this trial:** 20<br>**Number randomised to treatment group:** 10 (55% men; mean age 69.65 ± 5.81)<br>**Number randomised to control group:** 10** (55% men; mean age 68.70 ± 8.94)<br>**Total number included in final analysis:** 20<br>**Number included in treatment group for final analysis:** 10<br>**Number included in control group for final analysis:** 10** |


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**Yan 2010b** *(Continued)*

| | |
|---|---|
| Interventions | **Treatment:** low-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy. Low rTMS frequency: 1 Hz; intensity: 110% motor threshold; location: left DLPFC; 1 sequence included continuous stimulations for 30 minutes; frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Control:** sham rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy. Sham rTMS 0 Hz; intensity: 0; location: left or right DLPFC; 1 sequence included continuous stimulations for 30 minutes; frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Duration:** 7 days<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br><br>**Secondary outcomes**<br><br>• Adverse events<br>• Leaving the trial early<br>• Death |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Yan 2010c**

| | |
|---|---|
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** high-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br><br>**Control arm:** routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** not reported<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995 and confirmation by brain CT or MRI stated<br><br>**Time since stroke:** < 6 months<br><br>**Inclusion criteria:** (1) right-handedness; (2) disease course < 6 months; (3) can sign informed consent<br><br>**Exclusion criteria:** (1) history of psychiatric illness or family history; (2) aphasia; (3) severe dementia; (4) severe physical illnesses, consciousness disturbance, or deafness, which influences the expression of depressed mood; (4) psychoactive or non-addiction-producing substance-induced depression; (5) various reasons to refuse trial or difficulty in finishing trial<br><br>**Depression criteria:** depression diagnosed according to the CCMD-3 |


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**Yan 2010c** *(Continued)*

| | |
|---|---|
| | **Total number randomised in this trial:** 20<br><br>**Number randomised to treatment group:** 10 (50% men; mean age 68.65, SD 7.62)<br><br>**Number randomised to control group:** 10** (60% men; mean age 67.25, SD 9.15)<br><br>**Total number included in final analysis:** 20<br><br>**Number included in treatment group for final analysis:** 10<br><br>**Number included in control group for final analysis:** 10** |
| Interventions | **Treatment:** high-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy. High rTMS frequency: 10 Hz; intensity: 110% motor threshold; location: left DLPFC; 1 sequence included continuous stimulations for 30 minutes; frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Control:** routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br><br>**Duration:** 7 days<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br><br>**Secondary outcomes**<br><br>• Adverse events<br>• Leaving the trial early<br>• Death |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

**Yan 2010d**

| | |
|---|---|
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** low-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br><br>**Control arm:** routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy |
| Participants | **Geographical location:** China<br>**Setting:** inpatient<br>**Stroke criteria:** not reported<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke formulated by the Fourth National Symposium on Cerebrovascular Disease in 1995 and confirmation by brain CT or MRI stated<br><br>**Time since stroke:** < 6 months<br><br>**Inclusion criteria:** (1) right-handedness; (2) disease course < 6 months; (3) can sign informed consent |


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**Yan 2010d** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** (1) history of psychiatric illness or family history; (2) aphasia; (3) severe dementia; (4) severe physical illness, consciousness disturbance, or deafness, which influences the expression of depressed mood; (4) psychoactive or non-addiction-producing substance-induced depression; (5) various reasons to refuse trial or difficulty in finishing trial<br><br>**Depression criteria:** depression diagnosed according to the CCMD-3<br><br>**Total numbers randomised in this trial:** 20<br><br>**Numbers randomised to treatment group:** 10 (55% men; mean age 69.65, SD 5.81)<br><br>**Numbers randomised to control group:** 10** (60% men; mean age 67.25, SD 9.15)<br><br>**Total numbers included in final analysis:** 20<br><br>**Numbers included in treatment group for final analysis:** 10<br><br>**Numbers included in control group for final analysis:** 10** |
| Interventions | **Treatment:** low-frequency rTMS + routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy. Low rTMS frequency: 1 Hz; intensity: 110% motor threshold; location: left DLPFC; 1 sequence included continuous stimulations for 30 minutes; frequency of treatment: 1 sequence a day during 09:00 to 10:00<br><br>**Control:** routine care + flupentixol and melitracen 10.5 mg/tablet, 1 tablet twice a day + psychotherapy<br><br>**Duration:** 7 days<br><br>**Follow-up:** none |
| Outcomes | **Primary outcomes**<br><br>• Depression measured using HDRS<br>• Impairment measured using NIHSS<br><br>**Secondary outcomes**<br><br>• Adverse events<br>• Leaving the trial early<br>• Death |
| Notes | Unable to obtain information to determine if the psychotherapy component of the intervention meets the review criteria for psychotherapy |

** Results for control group halved.
ACA: anterior cerebral artery.
BDI: Beck Depression Inventory.
BI: Barthel Index.
CCMD-2-R: Chinese Classification of Mental Disorders, Second Edition, Revised.
CCMD-3: Chinese Classification of Mental Disorders, Third Edition.
CNS: central nervous system.
CSS: Chinese Stroke Scale.
CT: computed tomography.
DLPFC: dorsolateral pre-frontal cortex.
HADS: Hospital Anxiety Depression Scale.
HARS: Hamilton Anxiety Rating Scale.
HDRS-17: 17-item Hamilton Depression Rating Scale.
HDRS-24: 24-item Hamilton Depression Rating Scale.
Hz: hertz.
ICD: International Classification of Diseases.
LSI: Life Satisfaction Index.


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MMSE: Mini Mental State Examination.
MRI: magnetic resonance imaging.
NIHSS: National Institute of Health Stroke Scale.
PCA: posterior cerebral artery.
rTMS: repetitive transcranial magnetic stimulation.
SD: standard deviation.
SNRI: selective norepinephrine reuptake inhibitor.
SSRI: selective serotonin reuptake inhibitor.
SSS: Scandinavian Stroke Scale.
TCA: tricyclic antidepressant.
ZDS: Zung Depression Scale.

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

### Kirkevold 2018

| | |
|---|---|
| Trial name or title | Promoting psychosocial well-being following stroke: study protocol for a randomised, controlled trial |
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** dialogue-based intervention<br><br>**Control arm:** usual care |
| Participants | **Geographical location:** Norway<br><br>**Setting:** mixed<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) adults over 18 years of age; (2) acute stroke within the last month before inclusion; (3) medically stable; (4) sufficient cognitive functioning to participate (assessed by physician/stroke team); (5) interested in participating; (6) able to understand and speak Norwegian; (7) able to give informed consent<br><br>**Exclusion criteria:** (1) serious somatic or psychiatric disease, as these are assumed to impact ability to participate in the intervention; (2) severe dementia; (3) significant impressive aphasia or severe expressive aphasia<br><br>**Depression criteria:** no criteria for depression at entry |
| Interventions | **Treatment:** dialogue-based intervention to promote psychosocial well-being. Intervention consists of 8 one to one and a half hour dialogue-based sessions between the stroke survivor and a specially trained health professional (RN or OT). Each meeting has a guiding topical outline, which addresses significant issues described in the research literature (e.g. bodily changes, emotional challenges, personal relations, daily life issues, meaningful activities, existential issues, important values)<br><br>**Administered by:** trained health professional (RN or OT)<br><br>**Supervision:** not reported<br><br>**Control:** usual care<br><br>**Duration:** 6 months<br><br>**Follow-up:** 2 weeks |
| Outcomes | **Primary outcome** |


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**Kirkevold 2018** *(Continued)*

| | |
|---|---|
| | • Depression measured using GHQ-28<br><br>**Secondary outcomes**<br><br>• Coherence measured using SOC-13<br>• Health-related quality of life measured using SAQoL-39 |
| Starting date | December 2014 |
| Contact information | Dr. Marit Kirkevold, Institute of Health and Society and Research Center for Rehabilitation and Rehabilitation services and models (CHARM), University of Oslo, PO Box 1130, Blindern, 0318 Oslo, Norway<br><br>Email: marit.kirkevold@medisin.uio.no |
| Notes | |

**NCT03056287**

| | |
|---|---|
| Trial name or title | Exercise and brain stimulation for post-stroke |
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS<br><br>**Control arm:** Sham rTMS |
| Participants | **Geographical location:** USA<br><br>**Setting:** unclear<br><br>**Stroke criteria:** unclear<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) major depressive disorder (PHQ-9 > 10); (2) no antidepressant medications or clinically able to discontinue medications<br><br>**Exclusion criteria:** (1) unable to ambulate at least 150 feet before stroke, or experienced intermittent claudication while walking; (2) history of congestive heart failure, unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnoea at rest or during ADLs; (3) history of oxygen dependence; (4) pre-existing neurological disorders, dementia, or previous stroke; (5) history of major head trauma; (6) legal blindness or severe visual impairment; (7) history of psychosis or other Axis I disorder that is primary; (8) life expectancy < 1 year; (9) severe arthritis or other problem that limits passive range of motion; (10) history of DVT or pulmonary embolism within 6 months; (11) uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions; (12) severe hypertension with systolic > 200 mmHg and diastolic > 110 mmHg at rest; (13) suicide attempt in the last 2 years or at suicidal risk as assessed by SCID interview; (14) previous or current enrolment in a clinical trial to enhance motor recovery; (15) currently exercising ≥ 2 times per week (≥ 20 minutes); (16) presence of non-MRI compatible implants, pregnancy, or severe claustrophobia<br><br>**Depression criteria:** PHQ-9 > 10 and diagnosed according to DSM-IV |
| Interventions | **Treatment:** rTMS<br><br>**Control:** sham rTMS |


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**NCT03056287** *(Continued)*

| | |
|---|---|
| | **Duration:** 8 weeks<br><br>**Follow-up:** 8 weeks |
| Outcomes | **Primary outcome**<br><br>• Depression measured using HDRS<br><br>**Secondary outcome**<br><br>• Walking speed |
| Starting date | 1 January 2016 |
| Contact information | Dr. Chris Gregory, Medical University of South Carolina, Charleston, South Carolina, United States 29425<br><br>Email: gregoryc@musc.edu |
| Notes | |

**Tang 2017**

| | |
|---|---|
| Trial name or title | Repetitive transcranial magnetic stimulation for depression after basal ganglia ischaemic stroke: protocol for a multicentre randomised double-blind placebo-controlled trial |
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** active rTMS<br><br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** China<br><br>**Setting:** inpatient<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** clinical and MRI or CT findings of basal ganglia ischaemic stroke<br><br>**Inclusion criteria:** (1) first-time ischaemic stroke; (2) recent stroke (within 3 weeks to 3 months)<br><br>**Exclusion criteria:** (1) prior history of depressive disorders or major trauma within 1 year, severe depression, or any other severe mental disorder; (2) current or prior antidepressant use for any reason; (3) aphasia or severe cognitive impairment, severe hearing impairment, or severe language comprehension deficit due to other causes; (4) other cerebral disease such as Parkinson's disease, encephalitis, dementia, multiple sclerosis, head injury, severe systemic disease, or ongoing neoplasia; (5) ongoing postoperative recovery<br><br>**Depression criteria:** DSM-IV diagnosis of depression due to stroke (ICD-10-CM code 293.83 (F06.32)) |
| Interventions | **Treatment:** active rTMS<br><br>**Control:** sham rTMS<br><br>**Duration:** not reported |


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**Tang 2017** *(Continued)*

| | |
|---|---|
| | **Follow-up:** not reported |
| Outcomes | **Primary outcome**<br>• Depression measured using 24-item HDRS<br>**Secondary outcomes**<br>• Impairment measured using NIHSS<br>• Activities of Daily Living measured using ADLS<br>• Cognitive functioning measured using MoCA<br>• Aphasia measured using Aphasia Battery in Chinese, Social Support Revalued Scale |
| Starting date | 20 November 2017 |
| Contact information | Dr. Lianxu Zhao<br>Email: zhaolianxu@smu.edu.cn |
| Notes | |

**Thomas 2016**

| | |
|---|---|
| Trial name or title | BEhavioural Activation therapy for Depression after Stroke (BEADS): a study protocol for a feasibility randomised controlled pilot trial of a psychological intervention for post-stroke depression |
| Methods | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** behavioural activation therapy<br>**Control arm:** usual care |
| Participants | **Geographical location:** UK<br>**Setting:** mixed<br>**Number of participants:** unclear<br>**Stroke criteria:** ischaemic or haemorrhagic stroke<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** (1) minimum of 3 months and maximum of 5 years post stroke; (2) 18 years of age or older; (3) living in community settings (including nursing homes)<br>**Exclusion criteria:** (1) receiving medical or psychological treatment for depression at the time at which they had their stroke (based on self-report by patient/carer) and/or currently receiving psychological intervention; (2) diagnosis of dementia before the stroke (based on self-report by patient/carer); (3) communication difficulties that would impact their capacity to take part in the intervention; (4) visual or hearing impairment that would impact capacity to take part in the intervention (based on the therapist's discretion at baseline assessment); (5) unable to communicate in English before the stroke or without mental capacity to consent to take part in the trial<br>**Depression criteria:** PHQ-9 score ≥ 10. For participants with communication difficulties or severe cognitive difficulties who are unable to complete the PHQ-9, a score of at least 50/100 on VAMS Sad item |


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**Thomas 2016** *(Continued)*

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| Interventions | **Treatment:** behavioural activation (BA) therapy is a structured and individualised treatment that aims to increase people's level of activity, particularly the frequency of pleasant or enjoyable events, to improve mood. Maximum of 15 sessions of BA over 4 months, with an expected average of 10 sessions. Therapy sessions were face-to-face on an individual basis, at participants' residences, and lasted about 1 hour. A BA treatment manual was developed<br><br>**Administered by:** assistant psychologist<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** usual care<br><br>**Duration:** 4 months<br><br>**Follow-up:** 6 months |
| Outcomes | **Primary outcome**<br><br>• Depression measured using PHQ-9, SAD-Q Hospital version (observer-rated depression)<br><br>**Secondary outcomes**<br><br>• Activities of daily living measured using Nottingham Leisure Questionnaire<br>• Functional outcome measured using Nottingham EADL<br>• Health-related quality of life measured using EQ5D |
| Starting date | 12 December 2014 |
| Contact information | Dr. Shirley Thomas; Division of Rehabilitation and Ageing, School of Medicine, B Floor Medical School, Queens Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK<br><br>Email: shirley.thomas@nottingham.ac.uk |
| Notes | **Author contact:**emailed study authors to check if they can share findings (reply received: the funder has advised the author not to share findings until published 25 October 2018) |

**Xu 2016**

| | |
|---|---|
| Trial name or title | Efficacy and feasibility of antidepressant treatment in patients with post-stroke depression |
| Methods | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS<br><br>**Control arm:** sham rTMS |
| Participants | **Geographical location:** China<br><br>**Setting:** unclear<br><br>**Number of participants:** unclear<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** ischaemic brain region or infarction confirmed by CT or MRI |


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**Xu 2016** *(Continued)*

| | |
|---|---|
| | **Inclusion criteria:** (1) 2 weeks to 3 months after acute ischaemic stroke<br><br>**Exclusion criteria:** (1) all kinds of serious mental disorders other than depressive disorder; confirmed cases of various types of depression, or history of major mental trauma within 1 year; (2) verbal communication failure (aphasia, severe cognitive impairment, severe hearing loss, etc.); (3) other systemic diseases that have a serious impact on abilities of daily living; (4) brain disease other than stroke (such as Parkinson's disease, encephalitis, multiple sclerosis, brain trauma, etc.); (5) nuclear magnetic resonance or transcranial magnetic stimulation contraindications<br><br>**Depression criteria:** diagnostic criteria of depression disorder caused by other somatic disease accorded with American *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V, ICD-10-CM 293.83 (F06.32)) |
| Interventions | **Treatment:** rTMS<br><br>**Control:** sham rTMS<br><br>**Duration:** not reported<br><br>**Follow-up:** not reported |
| Outcomes | **Primary outcome**<br><br>• Depression measured using HDRS<br><br>**Secondary outcomes**<br><br>• Dependence measured using Social Support Revalued Scale<br>• Disability and impairments measured using Medical Coping Modes Questionnaire |
| Starting date | 1 January 2016 |
| Contact information | Dr. Suiyi Xu<br><br>Email: suiyixu@sina.com |
| Notes | **Author contact:** emailed study authors to check if there are any published results for the trial 3 December 2018; no reply received |

ADLs: activities of daily living.
ADLS: Activities of Daily Living Scale.
BA: behavioural activation.
CT: computed tomography.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
DSM-v: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
DVT: deep vein thrombosis.
EADL: Extended Activities of Daily Living.
EQ5D: EuroQoL 5-dimensions.
GHQ-28: 28-item General Health Questionnaire.
HDRS-24: 24-item Hamilton Depression Rating Scale.
ICD: International Classification for Diseases.
MoCA: Montreal Cognitive Assessment.
MRI: magnetic resonance imaging.
NIHSS: National Institutes of Health Stroke Scale.
OT: occupational therapist.
PHQ-9: 9-item Patient Health Questionnaire.
RN: registered nurse.
rTMS: repetitive transcranial magnetic stimulation.
SAD-Q: Stroke Aphasia Depression Questionnaire - hospital version.
SAQoL-39: Stroke Aphasia Quality of Life Scale.
SCID: severe combined immunodeficiency.


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SOC-13: Sense of Coherence.
VAMS: Visual Analog Mood Scale.

## DATA AND ANALYSES

### Comparison 1. Pharmacological interventions versus placebo

| 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 | 8 | 1025 | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.55, 0.88] |
| 1.1 Clinician interview/impression (number not improved) | 1 | 285 | Risk Ratio (M-H, Random, 95% CI) | 0.72 [0.54, 0.95] |
| 1.2 DSM-III | 1 | 39 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.32, 2.03] |
| 1.3 MADRS | 2 | 352 | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.59, 1.60] |
| 1.4 HDRS | 4 | 349 | Risk Ratio (M-H, Random, 95% CI) | 0.56 [0.46, 0.68] |
| 2 Depression: < 50% reduction in scale scores at end of treatment | 6 | 511 | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.32, 0.70] |
| 2.1 HDRS | 4 | 357 | Risk Ratio (M-H, Random, 95% CI) | 0.40 [0.25, 0.61] |
| 2.2 MADRS | 2 | 154 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.59, 1.01] |
| 3 Depression: average change in scores between baseline and end of treatment | 5 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.1 BDI (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 CGI (low score = improvement/high score = deterioration) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 HDRS (high score = more depressed) | 2 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 MADRS (high score = more depressed) | 3 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Depression: mean scores at end of treatment | 15 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 4.1 BDI (high score = more depressed) | 4 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 CGI (low score = improvement/high score = deterioration) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 HDRS (high score = more depressed) | 13 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.4 MADRS (high score = more depressed) | 2 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Melancholia scale (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.6 Zung Depression Scale (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Anxiety: meeting study criteria for anxiety at end of treatment | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5.1 Clinician interview/impression | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Cognitive function: 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) | 0.0 [0.0, 0.0] |
| 7 Cognitive function: 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) | 0.0 [0.0, 0.0] |
| 8 Activities of daily living: average change in scores between baseline and end of treatment | 2 | 256 | Mean Difference (IV, Random, 95% CI) | -8.0 [-24.18, 8.18] |
| 8.1 Barthel Index (high score = more dependent) | 2 | 256 | Mean Difference (IV, Random, 95% CI) | -8.0 [-24.18, 8.18] |
| 9 Activities of daily living: mean scores at end of treatment | 3 | 316 | Mean Difference (IV, Random, 95% CI) | 3.14 [-0.97, 7.26] |
| 9.1 Barthel Index (high score = more dependent) | 3 | 316 | Mean Difference (IV, Random, 95% CI) | 3.14 [-0.97, 7.26] |
| 10 Disability: average change in scores between baseline and end of treatment | 3 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 10.1 Functional Independence Measure (low score = dependence) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.2 Motoricity Index (low score = more motor impairment) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.3 Scandinavian Stroke Scale (low score = more neurological deficit) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.4 Rankin Scale (high score = more disability) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Disability: mean scores at end of treatment | 3 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 11.1 Functional Independence Measure (low score = dependence) | 2 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11.2 Motoricity Index (low score = more motor impairment) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11.3 Scandinavian Stroke Scale (low score = more neurological deficit) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Neurological function: average change in scores between baseline and 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) | 0.0 [0.0, 0.0] |
| 13 Neurological function: mean scores at end of treatment | 4 | 304 | Std. Mean Difference (IV, Random, 95% CI) | -0.95 [-1.44, -0.45] |
| 13.1 Chinese Stroke Scale (high score = more impairment) | 3 | 231 | Std. Mean Difference (IV, Random, 95% CI) | -1.15 [-1.59, -0.72] |
| 13.2 National Institutes of Health Stroke Scale (high score = more impairment | 1 | 73 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.87, 0.06] |
| 14 Adverse events: death | 9 | 848 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.20, 2.07] |
| 14.1 At end of treatment | 9 | 848 | Risk Ratio (M-H, Random, 95% CI) | 0.64 [0.20, 2.07] |
| 15 Adverse events: all | 10 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.1 Central nervous system events (e.g. confusion, sedation, tremor) | 5 | 488 | Risk Ratio (M-H, Fixed, 95% CI) | 1.55 [1.12, 2.15] |
| 15.2 Psychiatric events (e.g. anxiety, increased depression) | 3 | 183 | Risk Ratio (M-H, Fixed, 95% CI) | 0.28 [0.05, 1.70] |
| 15.3 Recurrent stroke | 3 | 195 | Risk Ratio (M-H, Fixed, 95% CI) | 1.51 [0.29, 7.76] |
| 15.4 Vascular events - not stroke (e.g. dizziness, palpitation) | 7 | 587 | Risk Ratio (M-H, Fixed, 95% CI) | 1.44 [0.94, 2.22] |
| 15.5 Gastrointestinal effects (e.g. constipation, diarrhoea) | 4 | 473 | Risk Ratio (M-H, Fixed, 95% CI) | 1.62 [1.19, 2.19] |
| 15.6 Other events - not listed above (e.g. dysuria, eye discomfort) | 7 | 638 | Risk Ratio (M-H, Fixed, 95% CI) | 1.32 [1.00, 1.75] |


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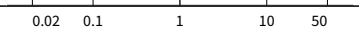
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 15.7 Protocol violation (e.g. refused treatment, withdrew consent) | 5 | 334 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.45, 2.68] |
| 16 Adverse events: leaving the study early (including death) | 13 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 16.1 All dropouts and withdrawals | 13 | 1165 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.82, 1.39] |

**Analysis 1.1. Comparison 1 Pharmacological interventions versus placebo, Outcome 1 Depression: meeting study criteria for depression at end of treatment.**

| Study or subgroup | Pharmacotherapy n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Clinician interview/impression (number not improved)** | | | | | |
| Ohtomo 1991 | 52/150 | 65/135 | | 17.87% | 0.72[0.54,0.95] |
| **Subtotal (95% CI)** | **150** | **135** | | **17.87%** | **0.72[0.54,0.95]** |
| Total events: 52 (Pharmacotherapy), 65 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.29(P=0.02) | | | | | |
| **1.1.2 DSM-III** | | | | | |
| Lipsey 1984 | 5/17 | 8/22 | | 5.12% | 0.81[0.32,2.03] |
| **Subtotal (95% CI)** | **17** | **22** | | **5.12%** | **0.81[0.32,2.03]** |
| Total events: 5 (Pharmacotherapy), 8 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.45(P=0.65) | | | | | |
| **1.1.3 MADRS** | | | | | |
| Murray 2002 | 7/62 | 4/61 | | 3.42% | 1.72[0.53,5.58] |
| Ponzio 2001 | 82/112 | 97/117 | | 22.15% | 0.88[0.77,1.01] |
| **Subtotal (95% CI)** | **174** | **178** | | **25.57%** | **0.98[0.59,1.6]** |
| Total events: 89 (Pharmacotherapy), 101 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0.07; $Chi^2$=1.39, df=1(P=0.24); $I^2$=27.92% | | | | | |
| Test for overall effect: Z=0.1(P=0.92) | | | | | |
| **1.1.4 HDRS** | | | | | |
| Andersen 1994 | 11/33 | 23/33 | | 10.75% | 0.48[0.28,0.81] |
| Fruehwald 2003 | 8/28 | 6/26 | | 5.18% | 1.24[0.5,3.09] |
| Wang 2005 | 24/54 | 45/54 | | 16.57% | 0.53[0.39,0.74] |
| Yang 2002 | 33/64 | 53/57 | | 18.94% | 0.55[0.43,0.71] |
| **Subtotal (95% CI)** | **179** | **170** | | **51.44%** | **0.56[0.46,0.68]** |
| Total events: 76 (Pharmacotherapy), 127 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0.01; $Chi^2$=3.36, df=3(P=0.34); $I^2$=10.78% | | | | | |
| Test for overall effect: Z=5.72(P<0.0001) | | | | | |
| **Total (95% CI)** | **520** | **505** | | **100%** | **0.7[0.55,0.88]** |
| Total events: 222 (Pharmacotherapy), 301 (Placebo) | | | | | |




Favours Pharmacotherapy — Favours Placebo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| Study or subgroup | Pharma-cotherapy n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Heterogeneity: Tau²=0.06; Chi²=21.68, df=7(P=0); I²=67.71% | | | | | |
| Test for overall effect: Z=3.03(P=0) | | | | | |
| Test for subgroup differences: Chi²=5.51, df=1 (P=0.14), I²=45.56% | | | | | |

Favours Pharmacotherapy 0.02 0.1 1 10 50 Favours Placebo

## Analysis 1.2. Comparison 1 Pharmacological interventions versus placebo, Outcome 2 Depression: < 50% reduction in scale scores at end of treatment.

| Study or subgroup | Pharma-cotherapy n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.2.1 HDRS** | | | | | |
| Andersen 1994 | 11/33 | 23/33 | | 16.06% | 0.48[0.28,0.81] |
| Lai 2006a | 18/40 | 34/40 | | 19.06% | 0.53[0.37,0.76] |
| Li 2008 | 20/60 | 22/30 | | 18.14% | 0.45[0.3,0.69] |
| Yang 2002 | 8/64 | 42/57 | | 13.73% | 0.17[0.09,0.33] |
| **Subtotal (95% CI)** | **197** | **160** | | **66.99%** | **0.4[0.25,0.61]** |
| Total events: 57 (Pharmacotherapy), 121 (Placebo) | | | | | |
| Heterogeneity: Tau²=0.14; Chi²=10.12, df=3(P=0.02); I²=70.37% | | | | | |
| Test for overall effect: Z=4.13(P<0.0001) | | | | | |
| **1.2.2 MADRS** | | | | | |
| Murray 2002 | 33/62 | 40/61 | | 20.24% | 0.81[0.6,1.09] |
| Wiart 2000 | 6/16 | 10/15 | | 12.77% | 0.56[0.27,1.16] |
| **Subtotal (95% CI)** | **78** | **76** | | **33.01%** | **0.77[0.59,1.01]** |
| Total events: 39 (Pharmacotherapy), 50 (Placebo) | | | | | |
| Heterogeneity: Tau²=0; Chi²=0.85, df=1(P=0.36); I²=0% | | | | | |
| Test for overall effect: Z=1.87(P=0.06) | | | | | |
| **Total (95% CI)** | **275** | **236** | | **100%** | **0.48[0.32,0.7]** |
| Total events: 96 (Pharmacotherapy), 171 (Placebo) | | | | | |
| Heterogeneity: Tau²=0.17; Chi²=21.51, df=5(P=0); I²=76.76% | | | | | |
| Test for overall effect: Z=3.73(P=0) | | | | | |
| Test for subgroup differences: Chi²=6.35, df=1 (P=0.01), I²=84.26% | | | | | |

Favours Pharmacotherapy 0.01 0.1 1 10 100 Favours Placebo

## Analysis 1.3. Comparison 1 Pharmacological interventions versus placebo, Outcome 3 Depression: average change in scores between baseline and end of treatment.

| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 BDI (high score = more depressed)** | | | | | | |
| Fruehwald 2003 | 28 | -6.1 (5.6) | 26 | -4.1 (6.5) | | -0.33[-0.86,0.21] |
| **1.3.2 CGI (low score = improvement/high score = deterioration)** | | | | | | |
| Fruehwald 2003 | 28 | -2.7 (1.6) | 26 | -2.1 (1.7) | | -0.36[-0.9,0.18] |

Favours Pharmacotherapy -5 -2.5 0 2.5 5 Favours Placebo


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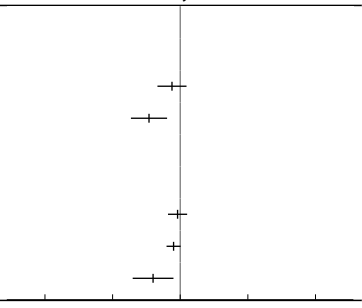
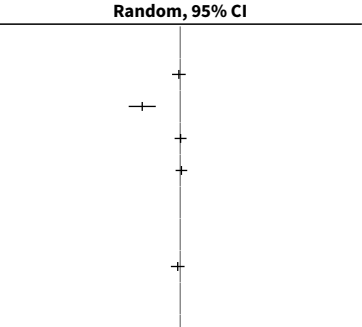
| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.3 HDRS (high score = more depressed)** | | | | | | |
| Fruehwald 2003 | 28 | -23.3 (12) | 26 | -19.1 (15.1) | | -0.3[-0.84,0.23] |
| Jiang 2001a | 30 | -20.1 (6.8) | 15 | -11.8 (7.5) | | -1.15[-1.82,-0.49] |
| **1.3.4 MADRS (high score = more depressed)** | | | | | | |
| Murray 2002 | 62 | -8.5 (8.9) | 61 | -7.6 (9.3) | | -0.1[-0.45,0.26] |
| Ponzio 2001 | 112 | -12 (9.5) | 117 | -9.9 (7.5) | | -0.25[-0.51,0.01] |
| Wiart 2000 | 16 | -16.6 (8.1) | 15 | -8.4 (7.8) | | -1[-1.76,-0.25] |




## Analysis 1.4. Comparison 1 Pharmacological interventions versus placebo, Outcome 4 Depression: mean scores at end of treatment.

| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.1 BDI (high score = more depressed)** | | | | | | |
| Fruehwald 2003 | 28 | 6.1 (5.6) | 26 | 6.8 (7.4) | | -0.11[-0.64,0.43] |
| Rampello 2005 | 16 | 8.1 (3.4) | 15 | 18.4 (3.3) | | -2.98[-4.04,-1.92] |
| Robinson 2008a | 48 | 9.1 (7.1) | 28 | 8.9 (7.3) | | 0.03[-0.44,0.49] |
| Robinson 2008b | 55 | 9.6 (7.5) | 28 | 8.9 (7.3) | | 0.09[-0.36,0.55] |
| **1.4.2 CGI (low score = improvement/high score = deterioration)** | | | | | | |
| Fruehwald 2003 | 28 | 3.1 (1.3) | 26 | 3.4 (1.7) | | -0.2[-0.73,0.34] |
| **1.4.3 HDRS (high score = more depressed)** | | | | | | |
| Andersen 1994 | 33 | 11.4 (5.1) | 33 | 14.1 (4.7) | | -0.54[-1.04,-0.05] |
| Fruehwald 2003 | 28 | 9.5 (7.9) | 26 | 11.2 (12.4) | | -0.16[-0.7,0.37] |
| Gao 2017a | 91 | 8.1 (2.4) | 45 | 8.5 (3.4) | | -0.14[-0.5,0.21] |
| Huang 2002 | 40 | 4.8 (0.6) | 40 | 16.3 (1.3) | | -11.33[-13.18,-9.47] |
| Jiang 2001a | 30 | 5.1 (3.1) | 15 | 13.2 (5.6) | | -1.95[-2.7,-1.2] |
| Kong 2007 | 48 | 12.6 (5.3) | 42 | 16.3 (3.7) | | -0.79[-1.22,-0.36] |
| Lai 2006a | 40 | 12.5 (8.4) | 40 | 21.5 (4.3) | | -1.34[-1.82,-0.85] |
| Li 2008 | 60 | 14.5 (2.4) | 30 | 18.7 (3.9) | | -1.4[-1.88,-0.91] |
| Lipsey 1984 | 17 | 2.8 (2.7) | 22 | 10 (8.1) | | -1.11[-1.79,-0.42] |
| Rampello 2005 | 16 | 9.3 (2.2) | 15 | 22.7 (2.4) | | -5.77[-7.46,-4.08] |
| Robinson 2008a | 48 | 10.2 (7.5) | 28 | 9.5 (6.6) | | 0.1[-0.37,0.56] |
| Robinson 2008b | 55 | 9.5 (6.6) | 28 | 9.5 (6.6) | | 0[-0.46,0.46] |
| Wang 2005 | 54 | 11.2 (4.3) | 54 | 15.3 (4.6) | | -0.93[-1.33,-0.53] |
| **1.4.4 MADRS (high score = more depressed)** | | | | | | |
| Murray 2002 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | | -0.16[-0.52,0.19] |
| Wiart 2000 | 16 | 11.8 (6.7) | 15 | 18.7 (10) | | -0.79[-1.53,-0.06] |
| **1.4.5 Melancholia scale (high score = more depressed)** | | | | | | |
| Andersen 1994 | 33 | 10.5 (5.1) | 33 | 12.9 (4.5) | | -0.49[-0.98,-0] |
| **1.4.6 Zung Depression Scale (high score = more depressed)** | | | | | | |
| Lipsey 1984 | 17 | 31 (10) | 22 | 42 (15.5) | | -0.81[-1.47,-0.15] |





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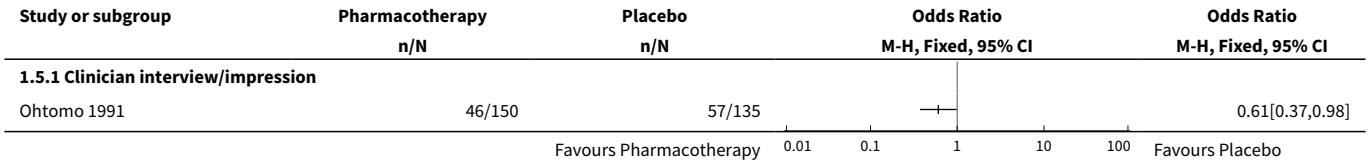
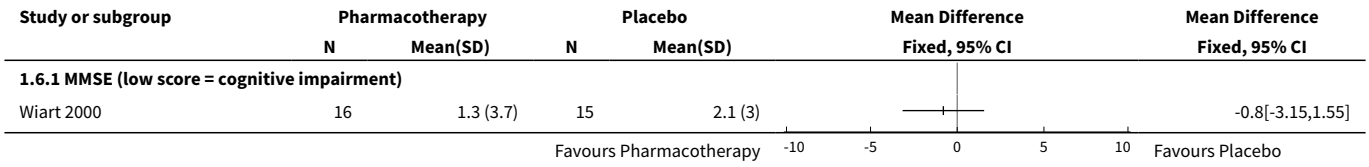
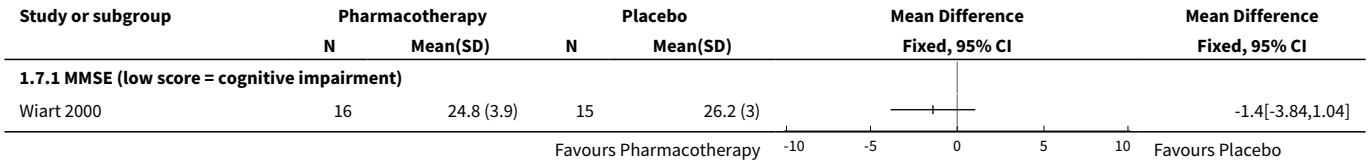
### Analysis 1.5. Comparison 1 Pharmacological interventions versus placebo, Outcome 5 Anxiety: meeting study criteria for anxiety at end of treatment.



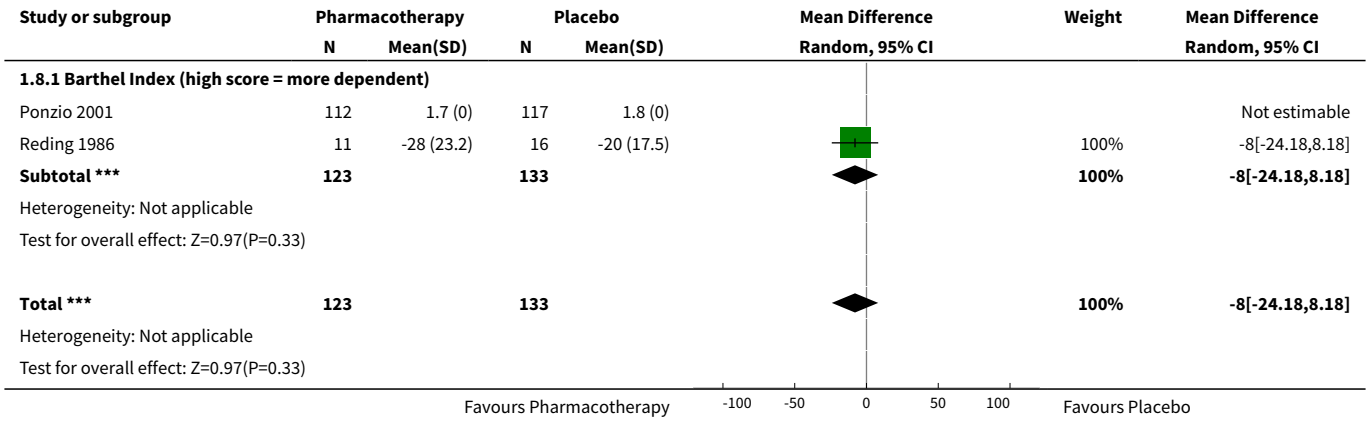

### Analysis 1.6. Comparison 1 Pharmacological interventions versus placebo, Outcome 6 Cognitive function: average change in scores between baseline and end of treatment.




### Analysis 1.7. Comparison 1 Pharmacological interventions versus placebo, Outcome 7 Cognitive function: mean scores at end of treatment.




### Analysis 1.8. Comparison 1 Pharmacological interventions versus placebo, Outcome 8 Activities of daily living: average change in scores between baseline and end of treatment.





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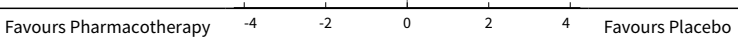
## Analysis 1.9. Comparison 1 Pharmacological interventions versus placebo, Outcome 9 Activities of daily living: mean scores at end of treatment.

| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.9.1 Barthel Index (high score = more dependent)** | | | | | | | |
| Gao 2017a | 91 | 71.5 (16.2) | 45 | 72.3 (15.9) | | 26.31% | -0.8[-6.51,4.91] |
| Kong 2007 | 48 | 60.4 (12.5) | 42 | 52.3 (13.5) | | 27.81% | 8.1[2.7,13.5] |
| Li 2008 | 60 | 40.8 (3.7) | 30 | 38.4 (5.8) | | 45.88% | 2.4[0.12,4.68] |
| **Subtotal ***** | **199** | | **117** | | | **100%** | **3.14[-0.97,7.26]** |
| Heterogeneity: Tau²=8.26; Chi²=5.34, df=2(P=0.07); I²=62.55% | | | | | | | |
| Test for overall effect: Z=1.5(P=0.13) | | | | | | | |
| **Total ***** | **199** | | **117** | | | **100%** | **3.14[-0.97,7.26]** |
| Heterogeneity: Tau²=8.26; Chi²=5.34, df=2(P=0.07); I²=62.55% | | | | | | | |
| Test for overall effect: Z=1.5(P=0.13) | | | | | | | |

## Analysis 1.10. Comparison 1 Pharmacological interventions versus placebo, Outcome 10 Disability: average change in scores between baseline and end of treatment.

| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.10.1 Functional Independence Measure (low score = dependence)** | | | | | | |
| Wiart 2000 | 16 | 24.7 (20.4) | 15 | 16.4 (23.2) | | 0.37[-0.34,1.08] |
| **1.10.2 Motoricity Index (low score = more motor impairment)** | | | | | | |
| Wiart 2000 | 16 | 18.9 (23.8) | 15 | 11.9 (26) | | 0.27[-0.43,0.98] |
| **1.10.3 Scandinavian Stroke Scale (low score = more neurological deficit)** | | | | | | |
| Fruehwald 2003 | 28 | 13.5 (7.4) | 26 | 15.4 (9.2) | | -0.22[-0.76,0.31] |
| **1.10.4 Rankin Scale (high score = more disability)** | | | | | | |
| Ponzio 2001 | 112 | -0.4 (0) | 117 | -0.4 (0) | | Not estimable |




## Analysis 1.11. Comparison 1 Pharmacological interventions versus placebo, Outcome 11 Disability: mean scores at end of treatment.

| Study or subgroup | Pharmacotherapy N | Pharmacotherapy Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.11.1 Functional Independence Measure (low score = dependence)** | | | | | | |
| Gao 2017a | 91 | 71.1 (17) | 45 | 71.5 (17.6) | | -0.4[-6.62,5.82] |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | | -1.3[-18.29,15.69] |
| **1.11.2 Motoricity Index (low score = more motor impairment)** | | | | | | |
| Wiart 2000 | 16 | 48.5 (24.6) | 15 | 55.3 (26.5) | | -6.8[-24.83,11.23] |
| **1.11.3 Scandinavian Stroke Scale (low score = more neurological deficit)** | | | | | | |

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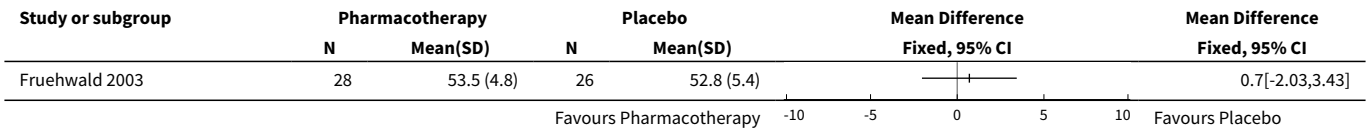
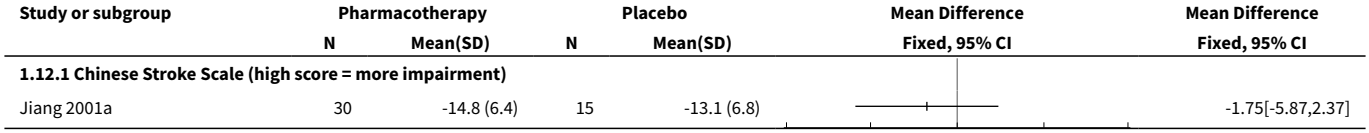
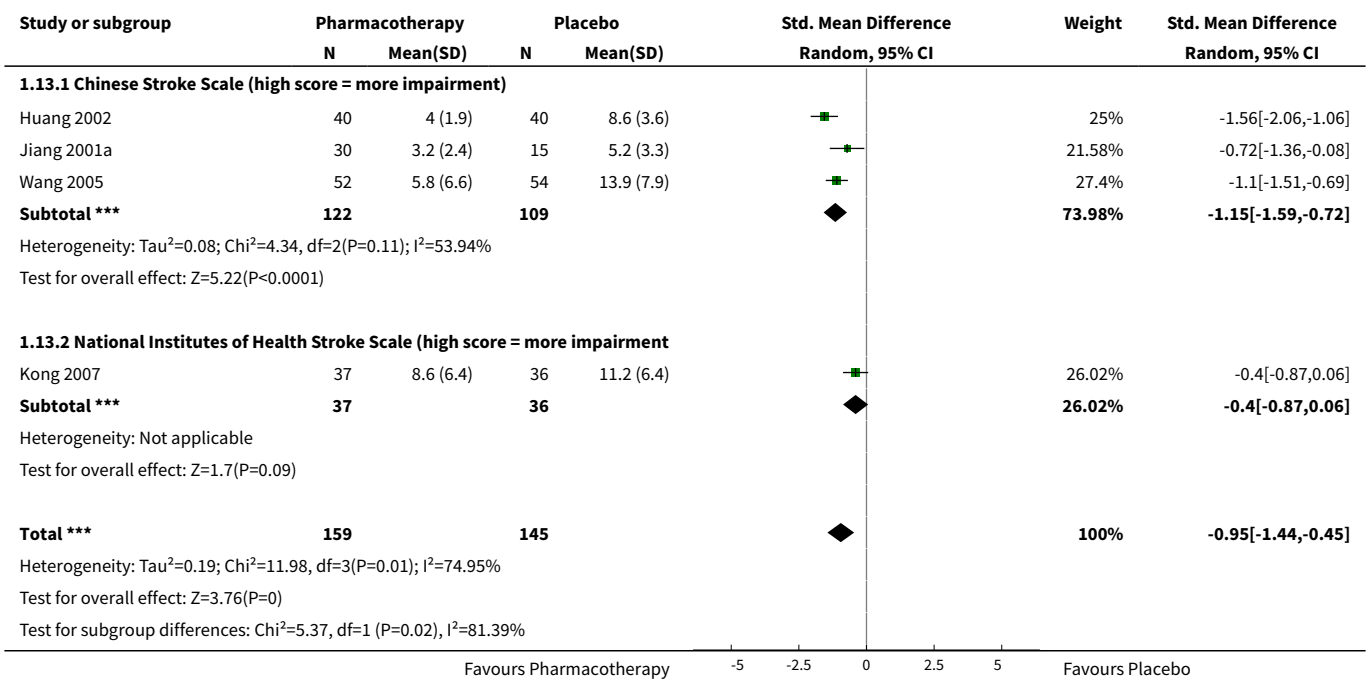


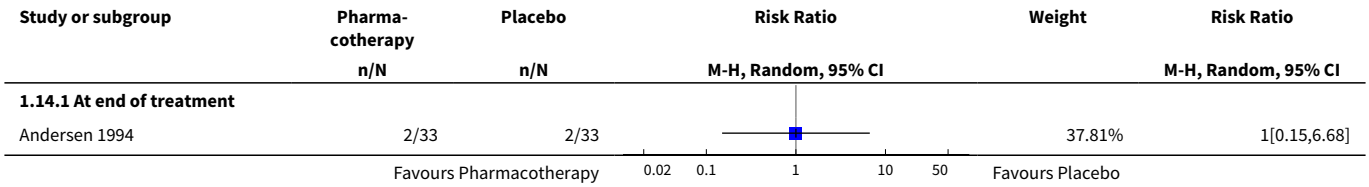

## Analysis 1.12. Comparison 1 Pharmacological interventions versus placebo, Outcome 12 Neurological function: average change in scores between baseline and end of treatment.




## Analysis 1.13. Comparison 1 Pharmacological interventions versus placebo, Outcome 13 Neurological function: mean scores at end of treatment.




## Analysis 1.14. Comparison 1 Pharmacological interventions versus placebo, Outcome 14 Adverse events: death.





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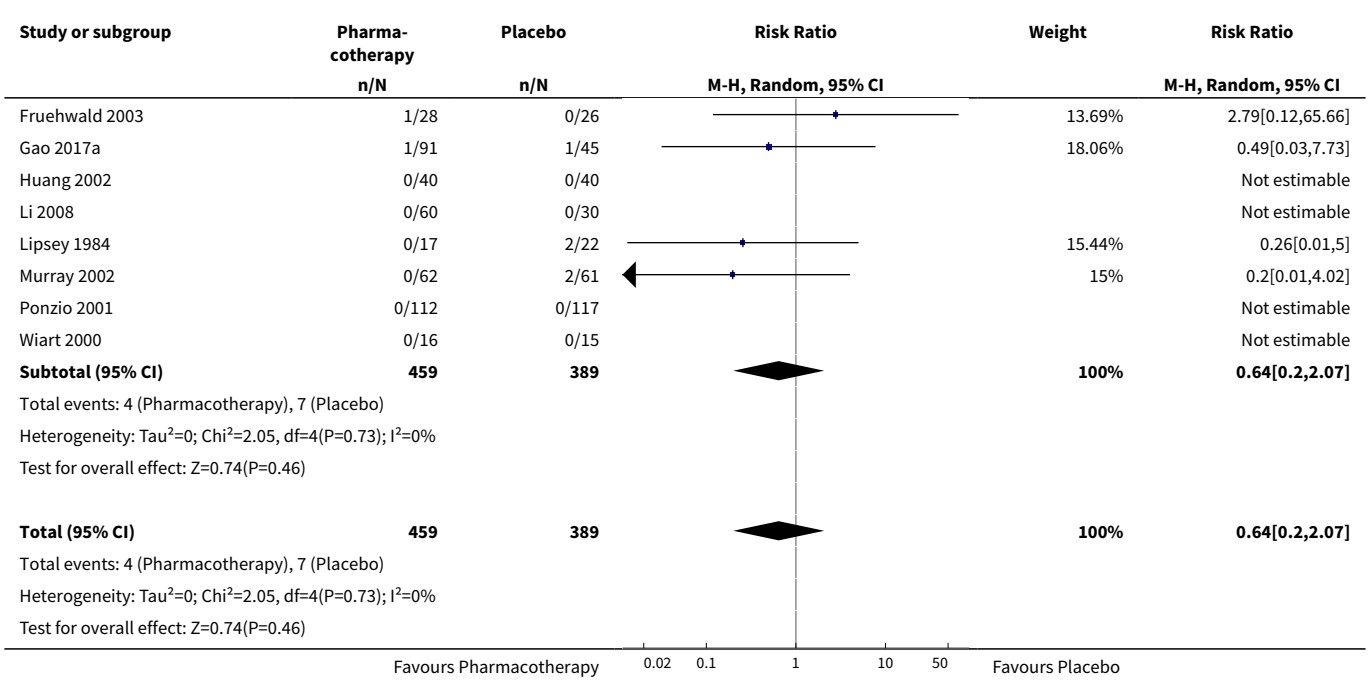
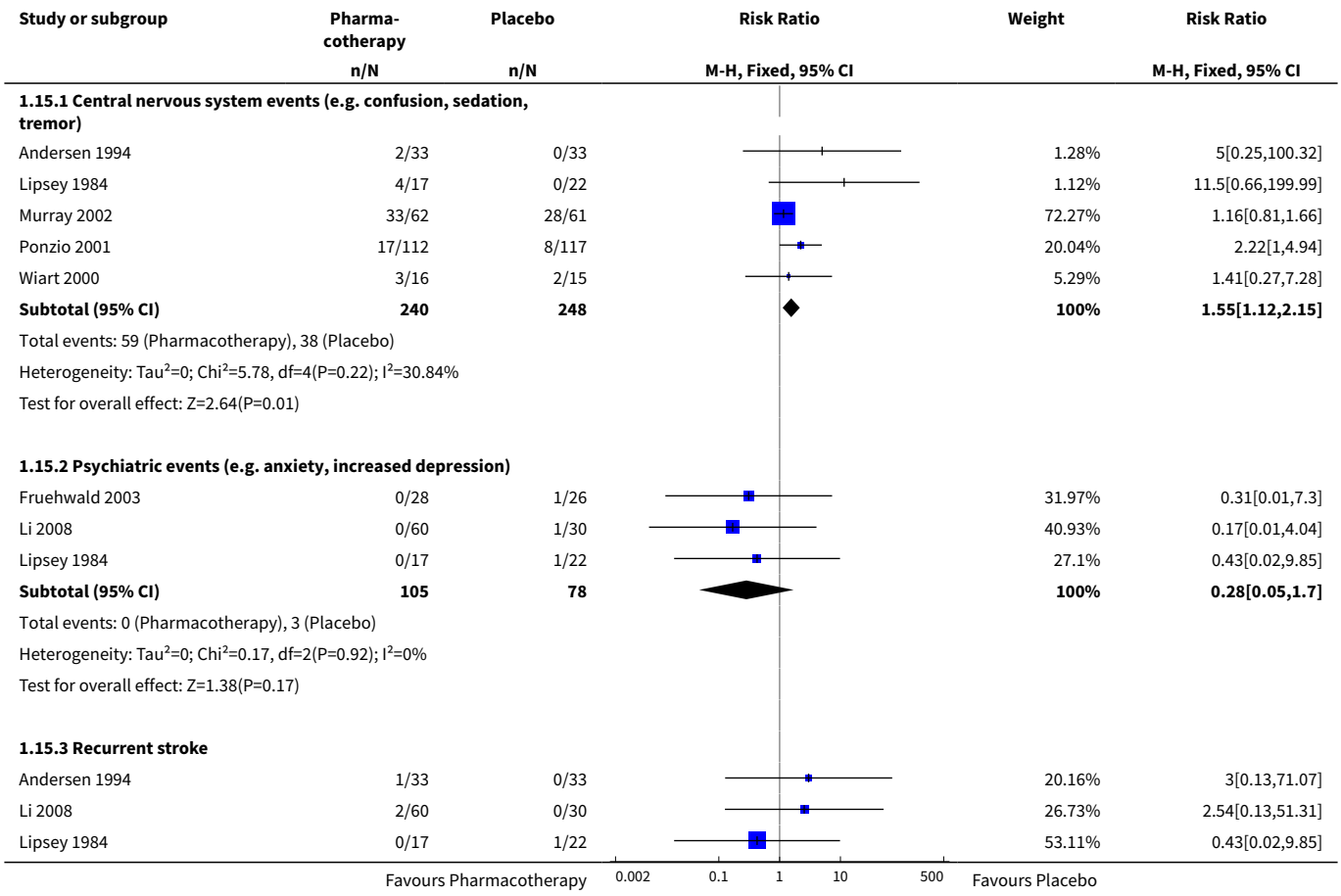



## Analysis 1.15. Comparison 1 Pharmacological interventions versus placebo, Outcome 15 Adverse events: all.





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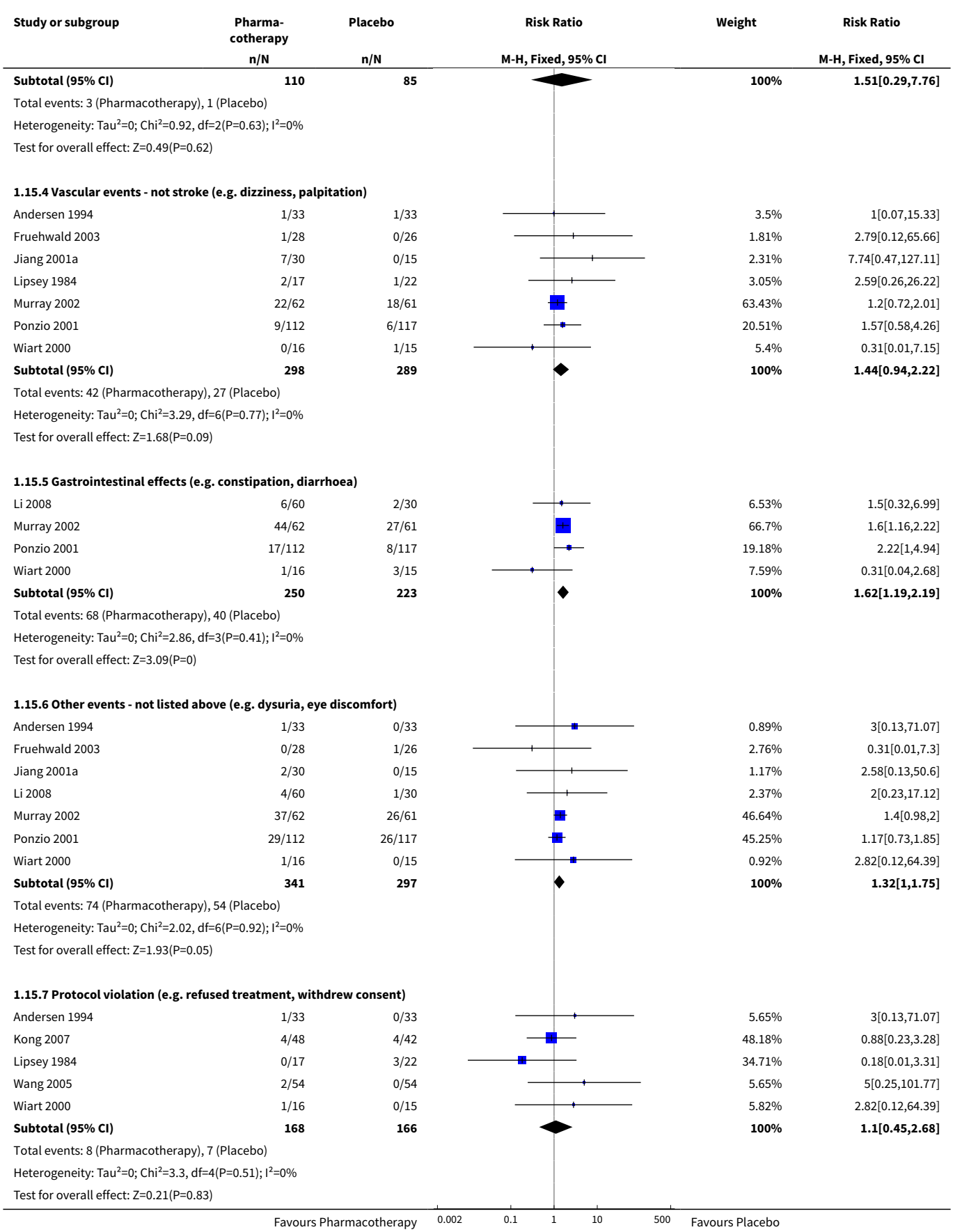



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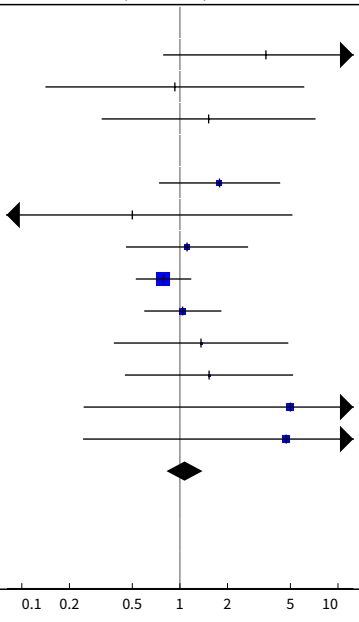
**Analysis 1.16. Comparison 1 Pharmacological interventions versus placebo, Outcome 16 Adverse events: leaving the study early (including death).**

| Study or subgroup | Pharma-cotherapy n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.16.1 All dropouts and withdrawals** | | | | | |
| Andersen 1994 | 7/33 | 2/33 | | 3.05% | 3.5[0.78,15.62] |
| Fruehwald 2003 | 2/28 | 2/26 | | 1.92% | 0.93[0.14,6.12] |
| Gao 2017a | 6/85 | 2/43 | | 2.81% | 1.52[0.32,7.21] |
| Huang 2002 | 0/40 | 0/40 | | | Not estimable |
| Kong 2007 | 11/37 | 6/36 | | 8.75% | 1.78[0.74,4.31] |
| Li 2008 | 2/60 | 1/15 | | 1.25% | 0.5[0.05,5.15] |
| Lipsey 1984 | 6/17 | 7/22 | | 8.65% | 1.11[0.46,2.7] |
| Murray 2002 | 24/62 | 30/61 | | 41.77% | 0.79[0.53,1.18] |
| Ponzio 2001 | 20/112 | 20/117 | | 21.5% | 1.04[0.59,1.83] |
| Robinson 2008a | 7/48 | 3/28 | | 4.23% | 1.36[0.38,4.85] |
| Robinson 2008b | 9/55 | 3/28 | | 4.54% | 1.53[0.45,5.2] |
| Wang 2005 | 2/54 | 0/54 | | 0.75% | 5[0.25,101.77] |
| Wiart 2000 | 2/16 | 0/15 | | 0.78% | 4.71[0.24,90.69] |
| **Subtotal (95% CI)** | **647** | **518** | | **100%** | **1.07[0.82,1.39]** |
| Total events: 98 (Pharmacotherapy), 76 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=9.38, df=11(P=0.59); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.49(P=0.62) | | | | | |




**Comparison 2. Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care**

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Depression: meeting study criteria for depression at end of treatment | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Depression: < 50% reduction in scale scores at end of treatment | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not select-ed |
| 2.1 HDRS | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Depression: mean scores at end of treatment | 8 | 495 | Mean Difference (IV, Random, 95% CI) | -6.63 [-9.71, -3.55] |
| 3.1 HDRS (high score = more de-pressed) | 8 | 495 | Mean Difference (IV, Random, 95% CI) | -6.63 [-9.71, -3.55] |
| 4 Depression: mean scores at end of follow-up | 3 | 170 | Mean Difference (IV, Random, 95% CI) | -2.60 [-3.33, -1.87] |
| 4.1 HDRS (high score = more de-pressed) | 3 | 170 | Mean Difference (IV, Random, 95% CI) | -2.60 [-3.33, -1.87] |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5 Activities of daily living: mean scores at end of treatment | 2 | 208 | Std. Mean Difference (IV, Random, 95% CI) | 1.84 [-1.40, 5.08] |
| 5.1 Barthel Index (high score = more dependent) | 1 | 108 | Std. Mean Difference (IV, Random, 95% CI) | 0.20 [-0.18, 0.57] |
| 5.2 ADL (high score = more impairment) | 1 | 100 | Std. Mean Difference (IV, Random, 95% CI) | 3.50 [2.87, 4.13] |
| 6 Neurological function: average change in scores between baseline and end of treatment | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6.1 Chinese Stroke Scale (high score = more impairment) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Neurological function: mean scores at end of treatment | 3 | 290 | Std. Mean Difference (IV, Random, 95% CI) | -2.21 [-3.32, -1.09] |
| 7.1 Chinese Stroke Scale (high score = more impairment) | 2 | 190 | Std. Mean Difference (IV, Random, 95% CI) | -1.79 [-2.94, -0.64] |
| 7.2 National Institutes of Health Stroke Scale (high score = more impairment) | 1 | 100 | Std. Mean Difference (IV, Random, 95% CI) | -3.04 [-3.63, -2.46] |
| 8 Adverse events: death | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.1 At end of treatment | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Adverse events: all | 2 | 496 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.1 Central nervous system events (e.g. confusion, sedation, tremor) | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.2 Gastrointestinal effects (e.g. constipation, diarrhoea) | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.3 Recurrent stroke | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.4 Other events - not listed above (e.g. dysuria, eye discomfort) | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Adverse events: leaving the study early (including death) | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.1 All dropouts and withdrawals | 2 | 124 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |


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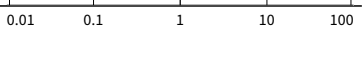
## Analysis 2.2. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 2 Depression: < 50% reduction in scale scores at end of treatment.

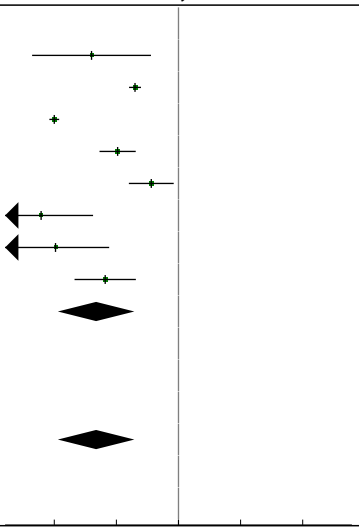
| Study or subgroup | Non-invasive stimulation n/N | Sham or usual care n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **2.2.1 HDRS** | | | | |
| Zheng 2016 | 39/41 | 29/41 | | 1.34[1.09,1.66] |




Favours Non-invasive stimulation — Favours Sham or usual care

## Analysis 2.3. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 3 Depression: mean scores at end of treatment.

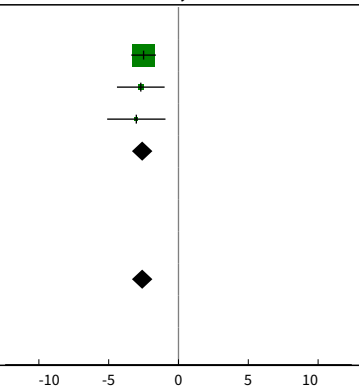
| Study or subgroup | Non-invasive stimulation N | Mean(SD) | Sham or usual care N | Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.3.1 HDRS (high score = more depressed)** | | | | | | | |
| Chen 2005a | 16 | 15.4 (6.7) | 16 | 22.4 (7.1) | | 10.44% | -7[-11.78,-2.22] |
| Gu 2016 | 12 | 6.8 (0.6) | 12 | 10.3 (0.6) | | 13.91% | -3.5[-3.98,-3.02] |
| Jiang 2014a | 50 | 7 (0.9) | 50 | 17 (1.1) | | 13.93% | -10[-10.39,-9.61] |
| Meng 2015 | 54 | 14.3 (4.5) | 54 | 19.2 (3.1) | | 13.54% | -4.9[-6.36,-3.44] |
| Yang 2013 | 19 | 12.9 (2.3) | 19 | 15.1 (3.3) | | 13.32% | -2.19[-3.99,-0.39] |
| Yang 2014a | 37 | 7.4 (2.8) | 19 | 18.5 (9.1) | | 11.1% | -11.06[-15.24,-6.88] |
| Yang 2014b | 37 | 8.6 (3.1) | 18 | 18.5 (9.1) | | 10.95% | -9.9[-14.22,-5.58] |
| Zheng 2016 | 41 | 13.3 (5.6) | 41 | 19.2 (5.8) | | 12.81% | -5.9[-8.37,-3.43] |
| **Subtotal ***** | **266** | | **229** | | | **100%** | **-6.63[-9.71,-3.55]** |
| Heterogeneity: $Tau^2$=17.7; $Chi^2$=467.16, df=7(P<0.0001); $I^2$=98.5% | | | | | | | |
| Test for overall effect: Z=4.22(P<0.0001) | | | | | | | |
| **Total ***** | **266** | | **229** | | | **100%** | **-6.63[-9.71,-3.55]** |
| Heterogeneity: $Tau^2$=17.7; $Chi^2$=467.16, df=7(P<0.0001); $I^2$=98.5% | | | | | | | |
| Test for overall effect: Z=4.22(P<0.0001) | | | | | | | |




Favours Non-invasive stimulation — Favours Sham or usual care

## Analysis 2.4. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 4 Depression: mean scores at end of follow-up.

| Study or subgroup | Non-invasive stimulation N | Mean(SD) | Sham or usual care N | Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.4.1 HDRS (high score = more depressed)** | | | | | | | |
| Gu 2016 | 12 | 7.8 (1.1) | 12 | 10.3 (1.1) | | 69.27% | -2.5[-3.38,-1.62] |
| Meng 2015 | 54 | 9.3 (2.2) | 54 | 12 (6) | | 18.42% | -2.7[-4.41,-0.99] |
| Yang 2013 | 19 | 7.1 (3.4) | 19 | 10.1 (3.2) | | 12.32% | -3.02[-5.11,-0.93] |
| **Subtotal ***** | **85** | | **85** | | | **100%** | **-2.6[-3.33,-1.87]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.22, df=2(P=0.9); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=6.96(P<0.0001) | | | | | | | |
| **Total ***** | **85** | | **85** | | | **100%** | **-2.6[-3.33,-1.87]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.22, df=2(P=0.9); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=6.96(P<0.0001) | | | | | | | |




Favours Non-invasive stimulation — Favours Sham or usual care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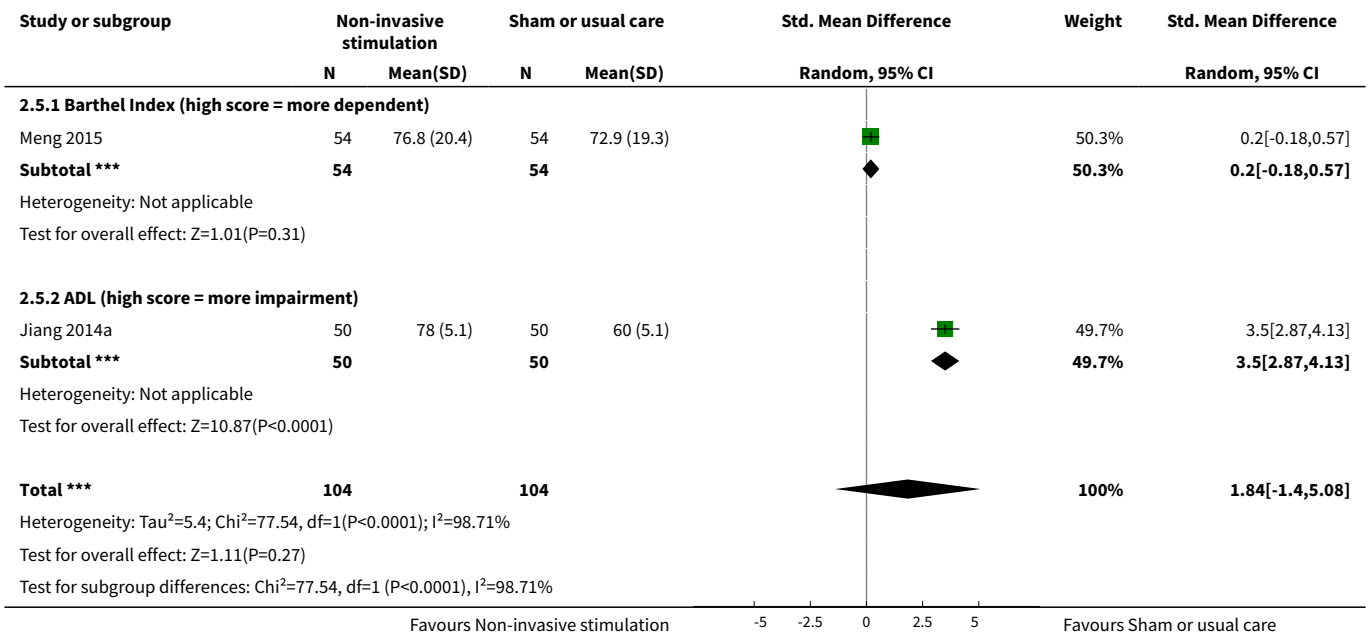
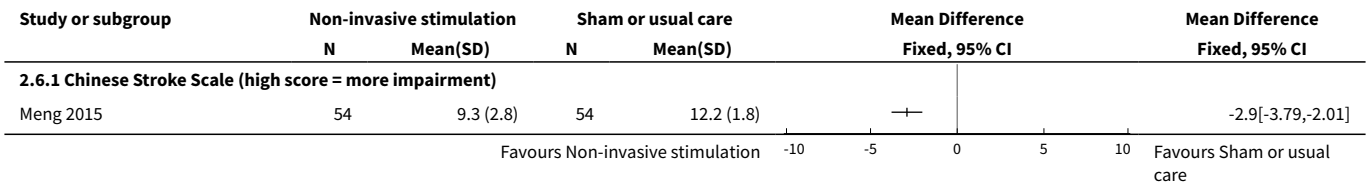
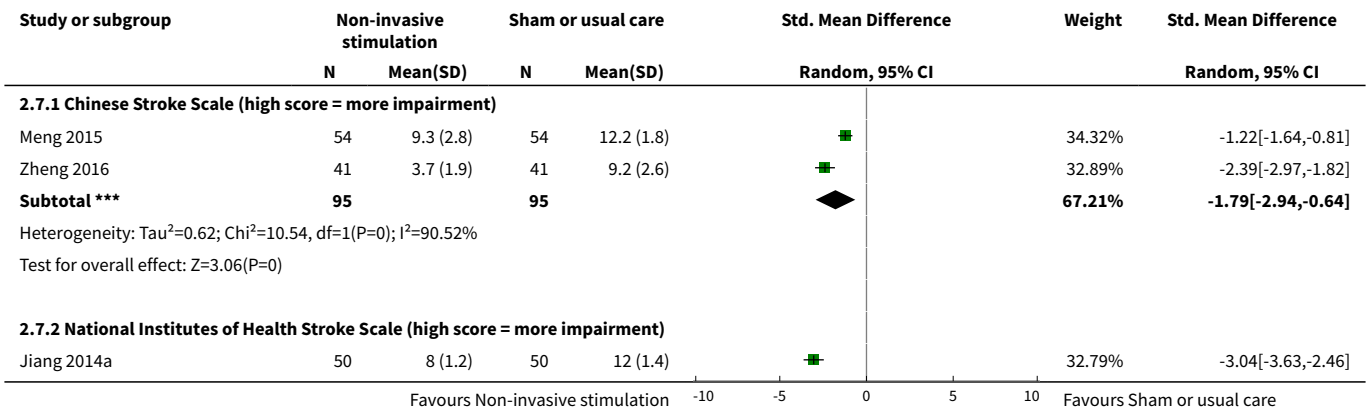
## Analysis 2.5. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 5 Activities of daily living: mean scores at end of treatment.




## Analysis 2.6. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 6 Neurological function: average change in scores between baseline and end of treatment.




## Analysis 2.7. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 7 Neurological function: mean scores at end of treatment.





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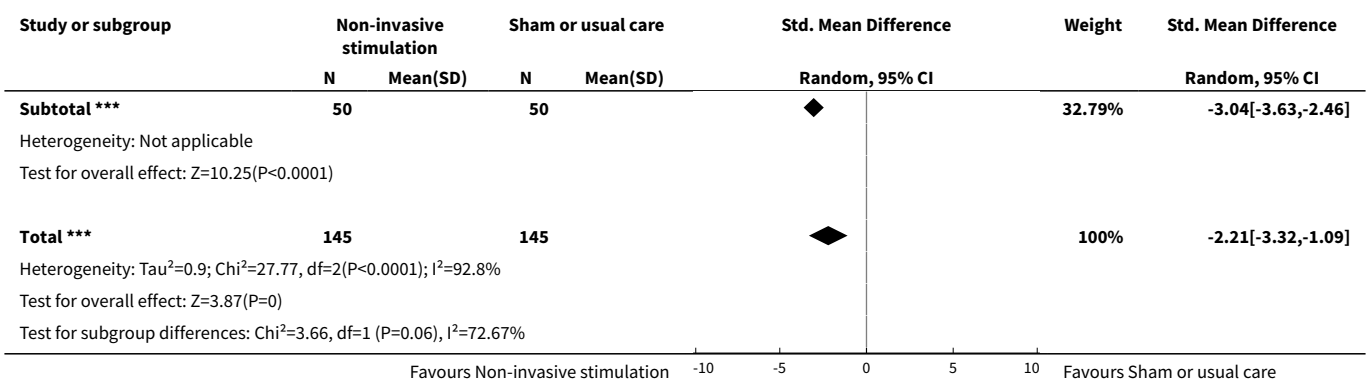
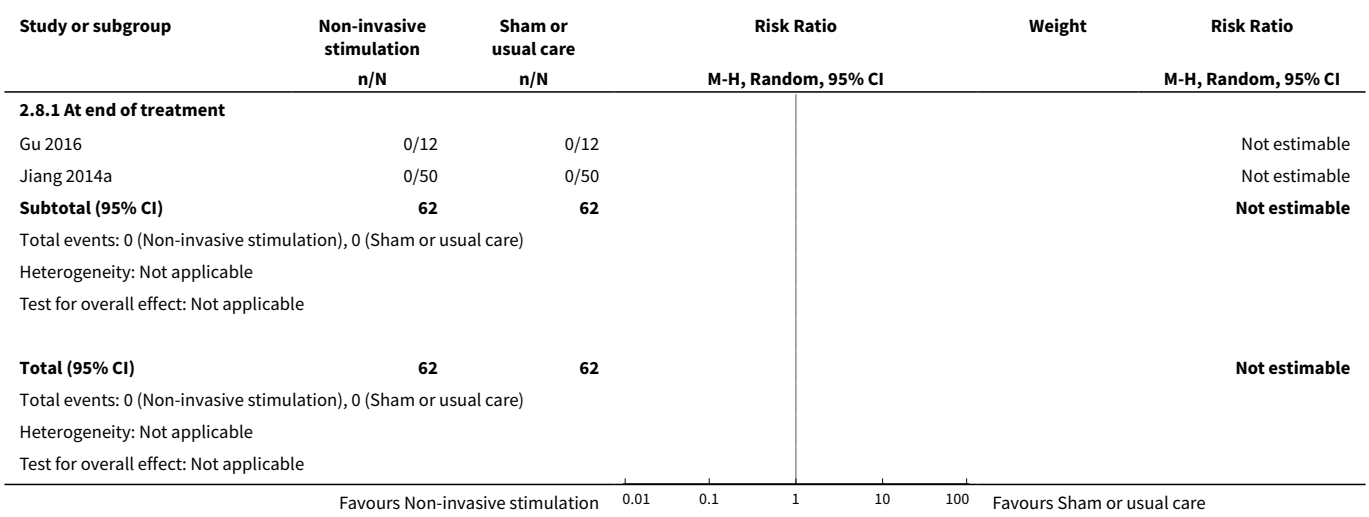
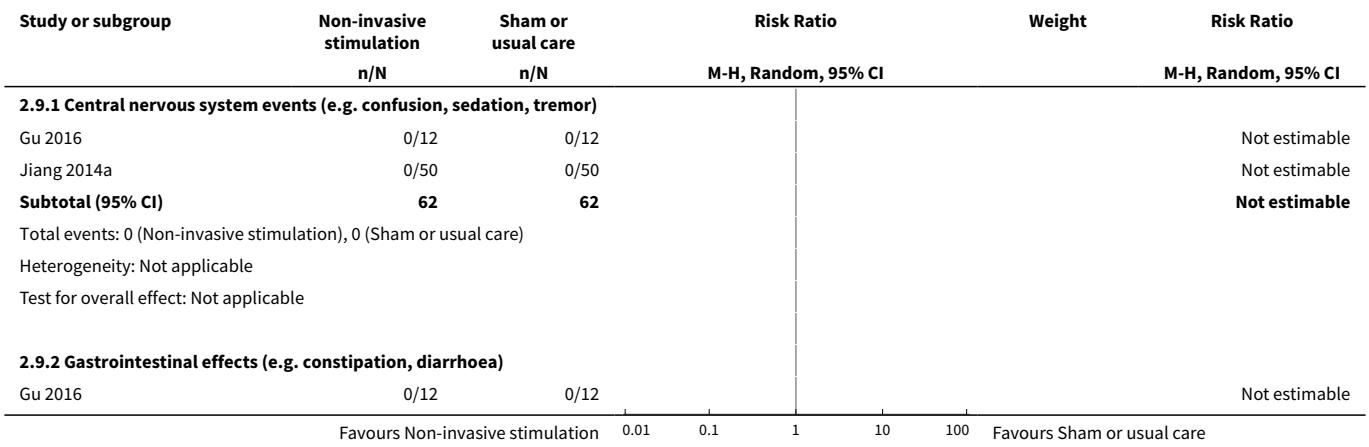



## Analysis 2.8. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 8 Adverse events: death.




## Analysis 2.9. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 9 Adverse events: all.





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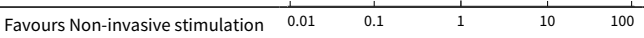
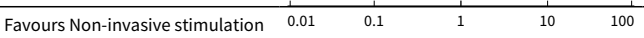
| Study or subgroup | Non-invasive stimulation n/N | Sham or usual care n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Jiang 2014a | 0/50 | 0/50 | | | Not estimable |
| **Subtotal (95% CI)** | **62** | **62** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **2.9.3 Recurrent stroke** | | | | | |
| Gu 2016 | 0/12 | 0/12 | | | Not estimable |
| Jiang 2014a | 0/50 | 0/50 | | | Not estimable |
| **Subtotal (95% CI)** | **62** | **62** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **2.9.4 Other events - not listed above (e.g. dysuria, eye discomfort)** | | | | | |
| Gu 2016 | 0/12 | 0/12 | | | Not estimable |
| Jiang 2014a | 0/50 | 0/50 | | | Not estimable |
| **Subtotal (95% CI)** | **62** | **62** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **Total (95% CI)** | **248** | **248** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| Test for subgroup differences: Not applicable | | | | | |




## Analysis 2.10. Comparison 2 Non-invasive brain stimulation versus sham non-invasive brain stimulation and/or usual care, Outcome 10 Adverse events: leaving the study early (including death).

| Study or subgroup | Non-invasive stimulation n/N | Sham or usual care n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **2.10.1 All dropouts and withdrawals** | | | | | |
| Gu 2016 | 0/12 | 0/12 | | | Not estimable |
| Jiang 2014a | 0/50 | 0/50 | | | Not estimable |
| **Subtotal (95% CI)** | **62** | **62** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **Total (95% CI)** | **62** | **62** | | | **Not estimable** |
| Total events: 0 (Non-invasive stimulation), 0 (Sham or usual care) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |





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**Comparison 3. Psychological therapy versus usual 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 | 6 | 521 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.62, 0.95] |
| 1.1 GHQ-28 (high score = greater psychological distress) | 1 | 254 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.76, 1.05] |
| 1.2 HDRS (high score = more depressed) | 4 | 225 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.54, 0.88] |
| 1.3 HADS (high score = more depressed) | 1 | 42 | Risk Ratio (M-H, Random, 95% CI) | 1.65 [0.16, 16.85] |
| 2 Depression: < 50% reduction in scale scores at end of treatment | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Depression: average change in scores between baseline and end of treatment | 3 | 189 | Mean Difference (IV, Random, 95% CI) | -6.20 [-8.24, -4.16] |
| 3.1 HDRS (high score = more depressed) | 3 | 189 | Mean Difference (IV, Random, 95% CI) | -6.20 [-8.24, -4.16] |
| 4 Depression: mean scores at end of treatment | 10 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 4.1 BDI (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 WDI (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 HDRS (high score = more depressed) | 5 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.4 SAD-Q 21-item (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Zung SDS (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.6 MADRS (high score= more depressed | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.7 HADS (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.8 Visual Analog Mood Scale (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.9 AHI (high score = more depressed | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.10 DASS-21 (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression: meeting study criteria for depression at end of follow-up | 3 | 201 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.59, 1.21] |
| 5.1 HDRS (high score = more depressed) | 3 | 201 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.59, 1.21] |
| 6 Depression: average change in scores between baseline and end of follow-up | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6.1 HDRS (high score = more depressed) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Depression: mean scores at end of follow-up | 5 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 7.1 BDI (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.2 WDI (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.3 SAD-Q 21-item (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.4 HDRS (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.5 HADS (high score = more depressed) | 2 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.6 MADRS (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.7 VAMS (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.8 PHQ-9 (high score = more depressed) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Psychological distress: average change in scores between baseline and end of treatment | 2 | 377 | Mean Difference (IV, Random, 95% CI) | -0.21 [-1.89, 1.48] |
| 8.1 GHQ-28 (high score = greater psychological distress) | 2 | 377 | Mean Difference (IV, Random, 95% CI) | -0.21 [-1.89, 1.48] |
| 9 Psychological distress: mean scores at end of treatment | 2 | 377 | Mean Difference (IV, Random, 95% CI) | -0.43 [-2.17, 1.31] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 GHQ-28 (high score = greater psychological distress) | 2 | 377 | Mean Difference (IV, Random, 95% CI) | -0.43 [-2.17, 1.31] |
| 10 Anxiety: meeting study criteria for anxiety at end of treatment | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.1 HADS Anxiety (high score = more anxious) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Anxiety: mean scores at end of treatment | 2 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.1 HADS Anxiety (high score = more anxious) | 2 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.2 State Trait Anxiety Inventory-Trait (high score = more anxious) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.3 State Trait Anxiety Inventory-State (high score = more anxious) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Anxiety: mean scores at end of follow-up | 1 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.1 State Trait Anxiety Inventory - Trait (high score = more anxious) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.2 State Trait Anxiety Inventory - State (high score = more anxious) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 13 Activities of daily living: average change in scores from baseline to end of treatment | 2 | 377 | Std. Mean Difference (IV, Random, 95% CI) | -0.03 [-0.24, 0.18] |
| 13.1 Nottingham EADL (high score = more independent) | 1 | 123 | Std. Mean Difference (IV, Random, 95% CI) | -0.10 [-0.48, 0.28] |
| 13.2 Barthel Index (high score = more dependent) | 1 | 254 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.25, 0.25] |
| 14 Activities of daily living: mean scores at end of treatment | 8 | | Std. Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 14.1 Barthel Index (high score = more dependent) | 8 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 14.2 Nottingham EADL (high score = more independent) | 1 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15 Activities of daily living: mean scores at end of follow-up | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 15.1 Modified Barthel Index (high score = more dependent) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |


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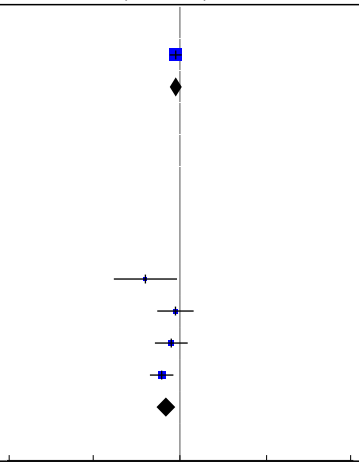
| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 16 Disability: mean scores at end of treatment | 2 | 162 | Std. Mean Difference (IV, Random, 95% CI) | -0.16 [-0.48, 0.17] |
| 16.1 WHODAS-II total | 1 | 24 | Std. Mean Difference (IV, Random, 95% CI) | -0.51 [-1.33, 0.30] |
| 16.2 FIM Motor | 1 | 138 | Std. Mean Difference (IV, Random, 95% CI) | -0.09 [-0.44, 0.27] |
| 17 Adverse events: death | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 17.1 At end of treatment | 8 | 831 | Risk Ratio (M-H, Random, 95% CI) | 0.65 [0.26, 1.66] |
| 18 Adverse events: all | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 18.1 Recurrent stroke | 1 | 254 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.24, 103.12] |
| 18.2 Vascular events - not stroke (e.g. transient ischaemic attack) | 1 | 254 | Risk Ratio (M-H, Random, 95% CI) | 0.71 [0.23, 2.19] |
| 18.3 Other events - not listed above (e.g. too ill) | 2 | 206 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.15, 6.81] |
| 18.4 Protocol violation (e.g. refused treatment, withdrew consent) | 3 | 250 | Risk Ratio (M-H, Random, 95% CI) | 1.08 [0.21, 5.50] |
| 19 Adverse events: leaving the study early (including death) | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 19.1 All dropouts and withdrawals | 8 | 784 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.42, 1.63] |

**Analysis 3.1. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 1 Depression: meeting study criteria for depression at end of treatment.**

| Study or subgroup | Psychotherapy n/N | Usual care/ attention cont n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **3.1.1 GHQ-28 (high score = greater psychological distress)** | | | | | |
| Watkins 2007 | 85/127 | 95/127 | | 39.68% | 0.89[0.76,1.05] |
| **Subtotal (95% CI)** | **127** | **127** | | **39.68%** | **0.89[0.76,1.05]** |
| Total events: 85 (Psychotherapy), 95 (Usual care/attention cont) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.38(P=0.17) | | | | | |
| **3.1.2 HDRS (high score = more depressed)** | | | | | |
| Alexopoulos 2012 | 4/12 | 10/12 | | 5.58% | 0.4[0.17,0.93] |
| Kirkness 2017a | 20/35 | 9/14 | | 13.75% | 0.89[0.55,1.44] |
| Kirkness 2017b | 21/37 | 10/14 | | 16.05% | 0.79[0.51,1.23] |
| Mitchell 2002 | 24/48 | 43/53 | | 24.12% | 0.62[0.45,0.84] |
| **Subtotal (95% CI)** | **132** | **93** | | **59.51%** | **0.69[0.54,0.88]** |
| Total events: 69 (Psychotherapy), 72 (Usual care/attention cont) | | | | | |





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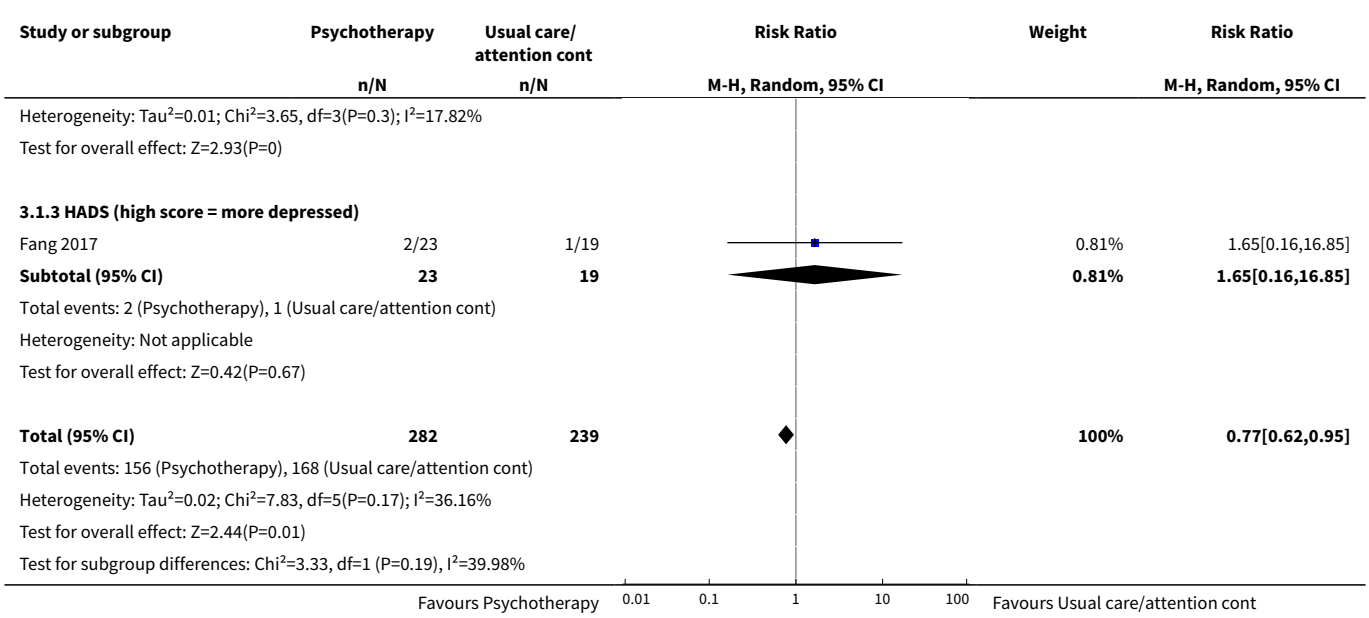
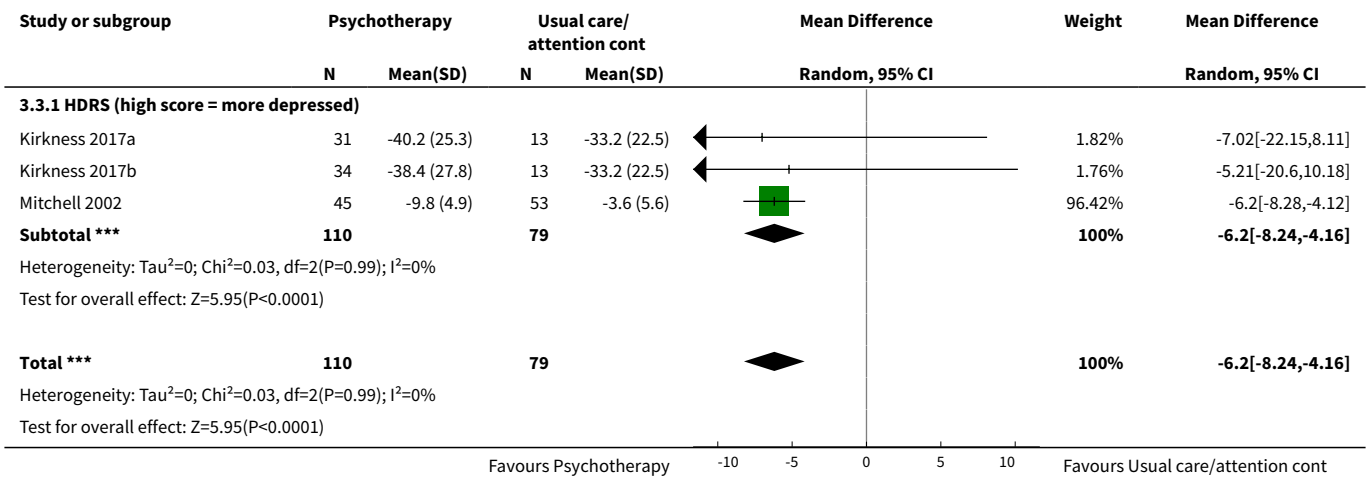
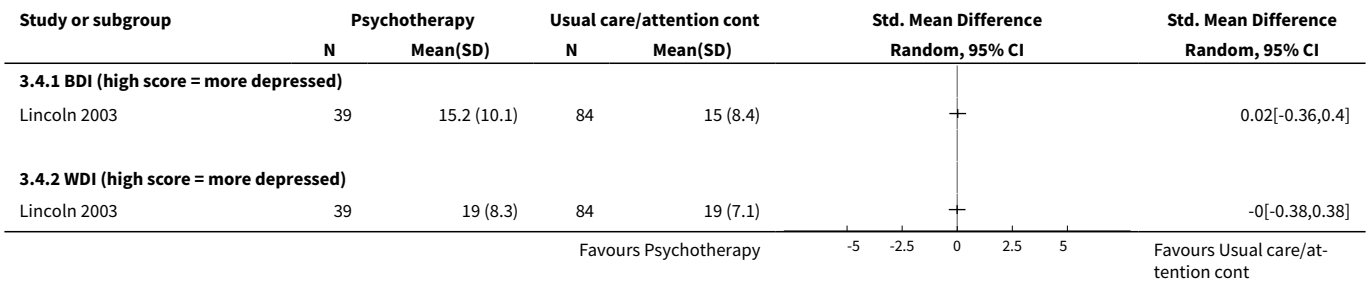



## Analysis 3.3. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 3 Depression: average change in scores between baseline and end of treatment.




## Analysis 3.4. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 4 Depression: mean scores at end of treatment.





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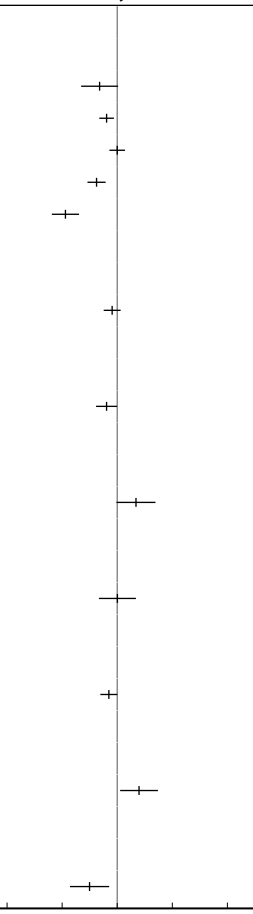
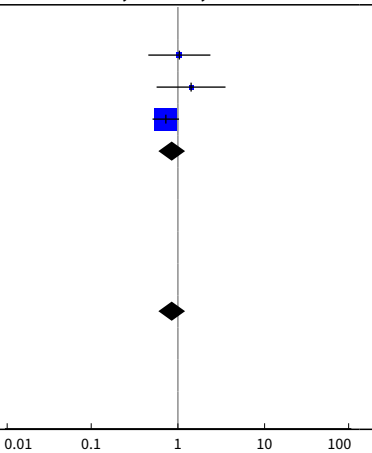
| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.4.3 HDRS (high score = more depressed)** | | | | | | |
| Alexopoulos 2012 | 12 | 8.2 (6.6) | 12 | 13.2 (5.4) | | -0.8[-1.64,0.04] |
| Cao 2009b | 72 | 36.2 (5) | 72 | 38.8 (5.7) | | -0.48[-0.81,-0.15] |
| Gao 2017b | 92 | 8.5 (2.7) | 46 | 8.5 (3.4) | | 0[-0.35,0.35] |
| Mitchell 2002 | 48 | 10.3 (5.3) | 53 | 16.2 (7) | | -0.94[-1.35,-0.53] |
| Zhao 2004 | 35 | 14.4 (3.1) | 35 | 21.1 (2.5) | | -2.35[-2.97,-1.73] |
| **3.4.4 SAD-Q 21-item (high score = more depressed)** | | | | | | |
| Thomas 2007 | 51 | 16.9 (10.2) | 54 | 19.2 (9.6) | | -0.23[-0.61,0.15] |
| **3.4.5 Zung SDS (high score = more depressed)** | | | | | | |
| Wang 2004a | 35 | 40.2 (7.6) | 35 | 44.2 (8.4) | | -0.48[-0.96,-0.01] |
| **3.4.6 MADRS (high score= more depressed** | | | | | | |
| Hoffmann 2015 | 12 | 19.4 (1.2) | 10 | 18.5 (0.7) | | 0.85[-0.03,1.74] |
| **3.4.7 HADS (high score = more depressed)** | | | | | | |
| Hoffmann 2015 | 12 | 8.2 (1.4) | 10 | 8.2 (0.9) | | 0.01[-0.83,0.85] |
| **3.4.8 Visual Analog Mood Scale (high score = more depressed)** | | | | | | |
| Thomas 2007 | 51 | 26.5 (22.3) | 54 | 36.3 (28.4) | | -0.38[-0.77,0.01] |
| **3.4.9 AHI (high score = more depressed** | | | | | | |
| Cullen 2018 | 12 | 2.7 (0.6) | 12 | 2.1 (0.6) | | 0.99[0.13,1.85] |
| **3.4.10 DASS-21 (high score = more depressed)** | | | | | | |
| Cullen 2018 | 12 | 13.5 (11.5) | 12 | 28.5 (11.6) | | -1.26[-2.15,-0.37] |




## Analysis 3.5. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 5 Depression: meeting study criteria for depression at end of follow-up.

| Study or subgroup | Psychotherapy n/N | Usual care/attention cont n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **3.5.1 HDRS (high score = more depressed)** | | | | | |
| Kirkness 2017a | 13/35 | 5/14 | | 17.04% | 1.04[0.46,2.37] |
| Kirkness 2017b | 15/37 | 4/14 | | 14.02% | 1.42[0.57,3.54] |
| Mitchell 2002 | 23/48 | 35/53 | | 68.94% | 0.73[0.51,1.03] |
| **Subtotal (95% CI)** | **120** | **81** | | **100%** | **0.85[0.59,1.21]** |
| Total events: 51 (Psychotherapy), 44 (Usual care/attention cont) | | | | | |
| Heterogeneity: $Tau^2$=0.02; $Chi^2$=2.25, df=2(P=0.32); $I^2$=11.17% | | | | | |
| Test for overall effect: Z=0.91(P=0.36) | | | | | |
| **Total (95% CI)** | **120** | **81** | | **100%** | **0.85[0.59,1.21]** |
| Total events: 51 (Psychotherapy), 44 (Usual care/attention cont) | | | | | |
| Heterogeneity: $Tau^2$=0.02; $Chi^2$=2.25, df=2(P=0.32); $I^2$=11.17% | | | | | |
| Test for overall effect: Z=0.91(P=0.36) | | | | | |





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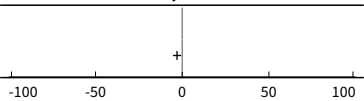
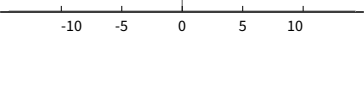
### Analysis 3.6. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 6 Depression: average change in scores between baseline and end of follow-up.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.6.1 HDRS (high score = more depressed)** | | | | | | |
| Mitchell 2002 | 48 | -9.2 (5.7) | 53 | -6.2 (6.4) | | -3[-5.36,-0.64] |



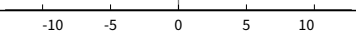

### Analysis 3.7. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 7 Depression: mean scores at end of follow-up.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.7.1 BDI (high score = more depressed)** | | | | | | |
| Lincoln 2003 | 39 | 14.3 (8) | 84 | 15.3 (8.7) | | -0.12[-0.5,0.26] |
| **3.7.2 WDI (high score = more depressed)** | | | | | | |
| Lincoln 2003 | 39 | 19.2 (7.3) | 84 | 19.7 (8.8) | | -0.06[-0.44,0.32] |
| **3.7.3 SAD-Q 21-item (high score = more depressed)** | | | | | | |
| Thomas 2007 | 51 | 17.4 (10) | 54 | 21.9 (9.5) | | -0.46[-0.85,-0.07] |
| **3.7.4 HDRS (high score = more depressed)** | | | | | | |
| Mitchell 2002 | 48 | 8.7 (6) | 53 | 11.3 (6.3) | | -0.41[-0.81,-0.02] |
| **3.7.5 HADS (high score = more depressed)** | | | | | | |
| Hoffmann 2015 | 12 | 4.6 (2.7) | 10 | 8.9 (1.7) | | -1.78[-2.81,-0.76] |
| Kerr 2018 | 4 | 4.5 (3.9) | 6 | 7 (2.7) | | -0.7[-2.03,0.62] |
| **3.7.6 MADRS (high score = more depressed)** | | | | | | |
| Hoffmann 2015 | 12 | 19.8 (1.8) | 10 | 18.7 (1.1) | | 0.73[-0.14,1.6] |
| **3.7.7 VAMS (high score = more depressed)** | | | | | | |
| Thomas 2007 | 51 | 25.5 (21.5) | 54 | 32.1 (29.3) | | -0.25[-0.64,0.13] |
| **3.7.8 PHQ-9 (high score = more depressed)** | | | | | | |
| Kerr 2018 | 4 | 1.7 (2.9) | 6 | 6 (7.4) | | -0.64[-1.95,0.68] |




### Analysis 3.8. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 8 Psychological distress: average change in scores between baseline and end of treatment.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.8.1 GHQ-28 (high score = greater psychological distress)** | | | | | | | |
| Lincoln 2003 | 39 | -6.2 (15.3) | 84 | -7 (15.3) | | 8.38% | 0.82[-4.99,6.63] |





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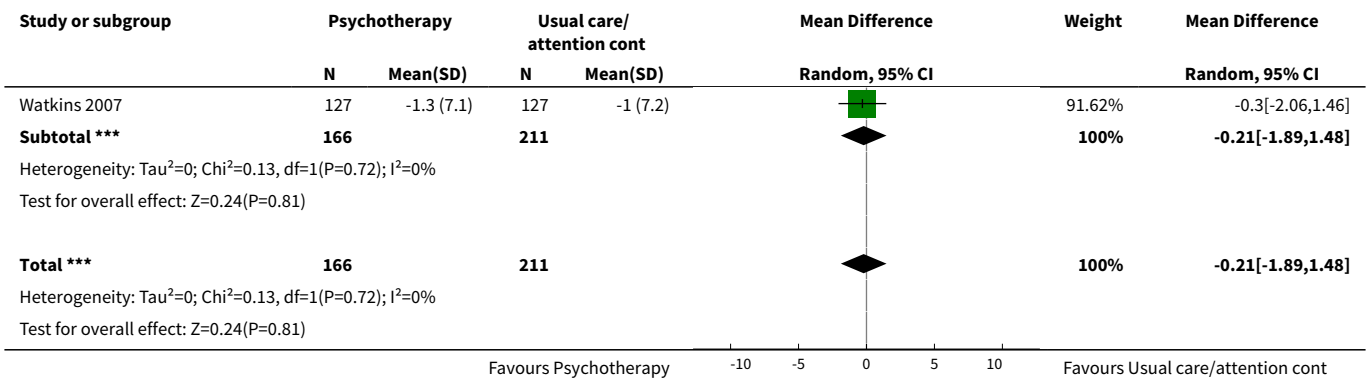
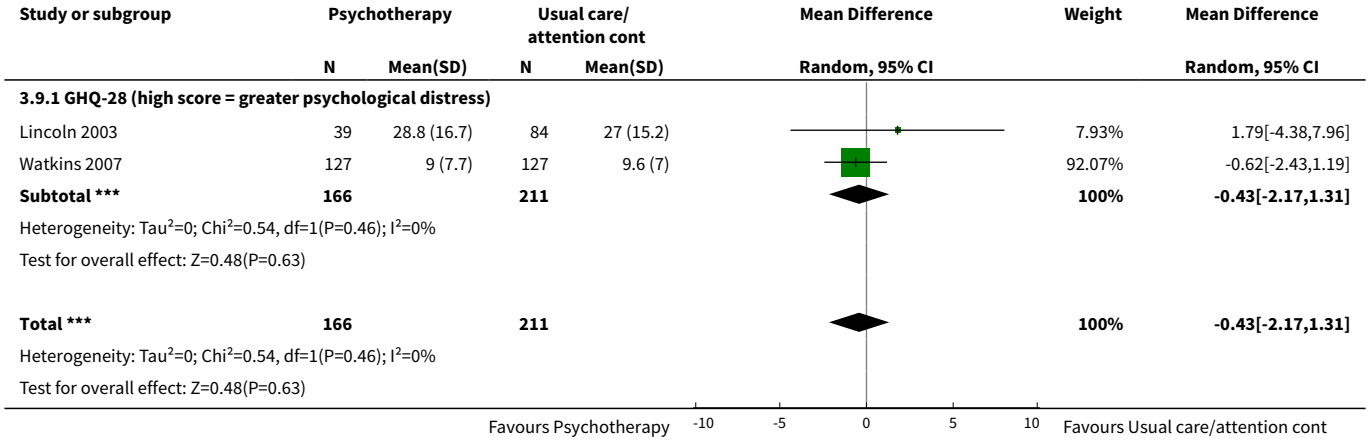
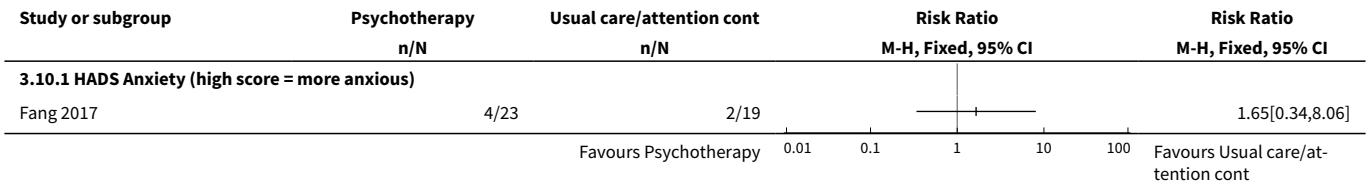


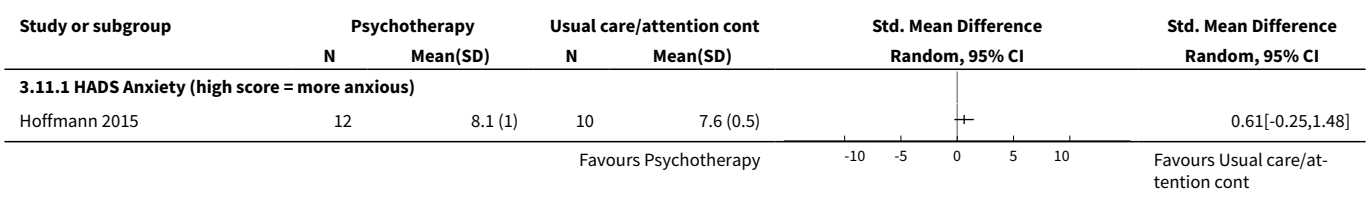

## Analysis 3.9. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 9 Psychological distress: mean scores at end of treatment.




## Analysis 3.10. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 10 Anxiety: meeting study criteria for anxiety at end of treatment.




## Analysis 3.11. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 11 Anxiety: mean scores at end of treatment.





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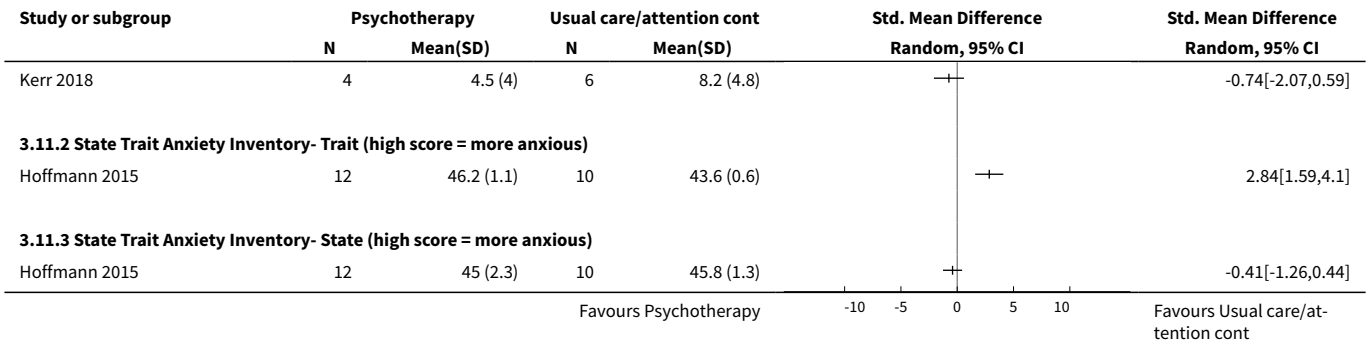
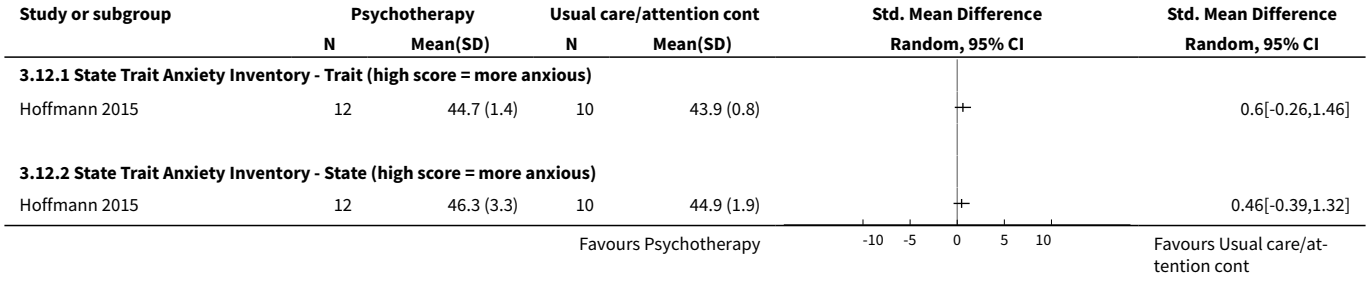
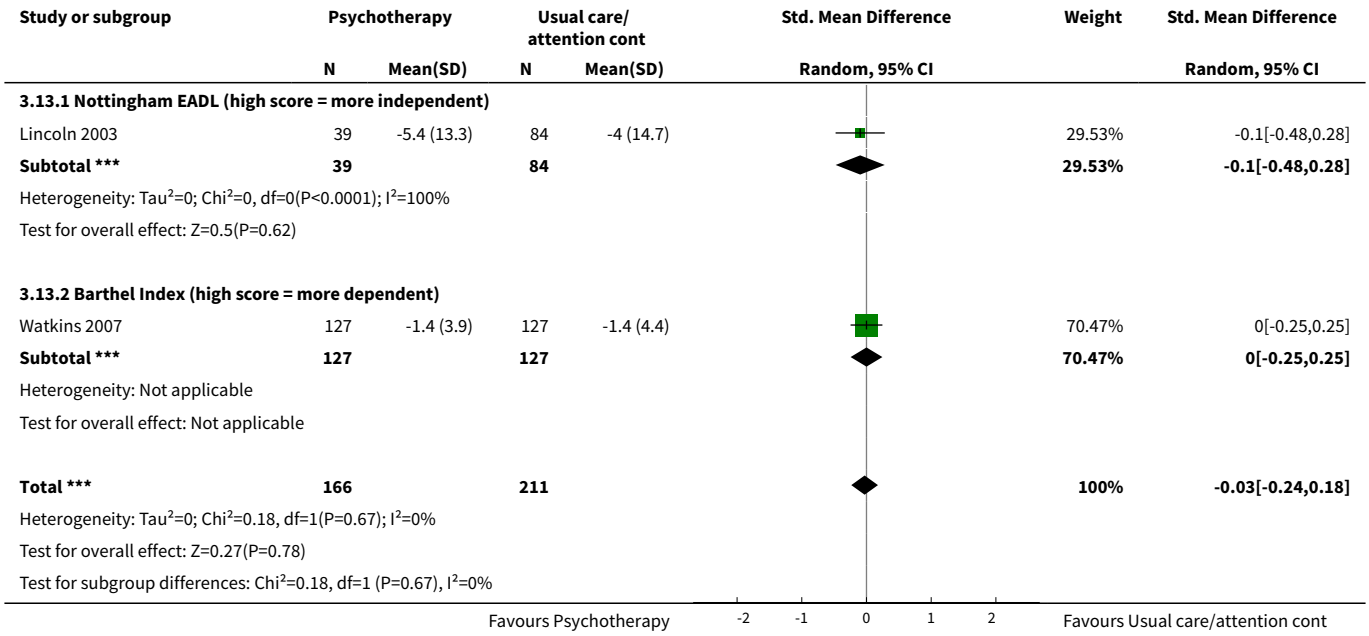



## Analysis 3.12. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 12 Anxiety: mean scores at end of follow-up.




## Analysis 3.13. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 13 Activities of daily living: average change in scores from baseline to end of treatment.





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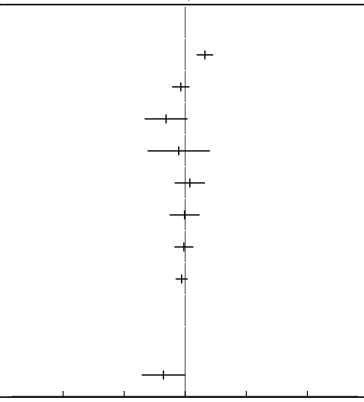
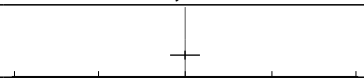
## Analysis 3.14. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 14 Activities of daily living: mean scores at end of treatment.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Std. Mean Difference Random, 95% CI | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.14.1 Barthel Index (high score = more dependent)** | | | | | | |
| Cao 2009b | 72 | 42.7 (8.3) | 72 | 36.3 (7.5) | | 0.8[0.46,1.14] |
| Gao 2017b | 92 | 69.3 (16.9) | 46 | 72.3 (15.9) | | -0.18[-0.53,0.17] |
| Hoffmann 2015 | 12 | 68.2 (2.8) | 10 | 70.2 (2.1) | | -0.78[-1.66,0.09] |
| Kerr 2018 | 4 | 95.7 (7.2) | 6 | 97.8 (7.1) | | -0.27[-1.54,1.01] |
| Kirkness 2017a | 35 | 94.7 (15) | 14 | 91.7 (17.3) | | 0.19[-0.43,0.81] |
| Kirkness 2017b | 37 | 91.2 (18.2) | 14 | 91.7 (17.3) | | -0.03[-0.64,0.59] |
| Mitchell 2002 | 48 | 85.5 (25.1) | 53 | 86.7 (17.9) | | -0.06[-0.45,0.34] |
| Watkins 2007 | 127 | 16.2 (4.3) | 127 | 16.8 (3.8) | | -0.15[-0.39,0.1] |
| **3.14.2 Nottingham EADL (high score = more independent)** | | | | | | |
| Hoffmann 2015 | 12 | 34.7 (6.5) | 10 | 39.7 (3.5) | | -0.89[-1.78,-0] |



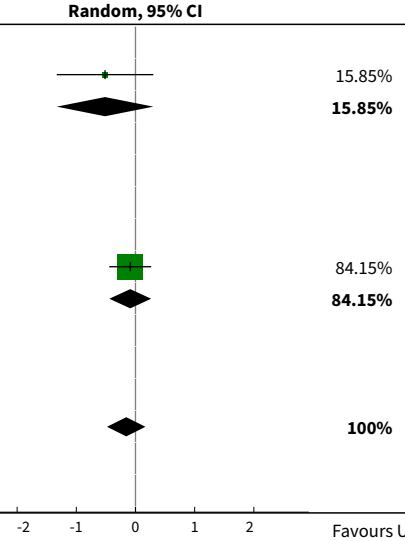

## Analysis 3.15. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 15 Activities of daily living: mean scores at end of follow-up.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.15.1 Modified Barthel Index (high score = more dependent)** | | | | | | |
| Hoffmann 2015 | 2 | 76.3 (5.6) | 5 | 76.4 (4.3) | | -0.12[-8.73,8.49] |




## Analysis 3.16. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 16 Disability: mean scores at end of treatment.

| Study or subgroup | Psychotherapy N | Psychotherapy Mean(SD) | Usual care/attention cont N | Usual care/attention cont Mean(SD) | Std. Mean Difference Random, 95% CI | Weight | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.16.1 WHODAS-II total** | | | | | | | |
| Alexopoulos 2012 | 12 | 24.5 (8.5) | 12 | 29.5 (10.2) | | 15.85% | -0.51[-1.33,0.3] |
| **Subtotal ***** | **12** | | **12** | | | **15.85%** | **-0.51[-1.33,0.3]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=1.24(P=0.22) | | | | | | | |
| **3.16.2 FIM Motor** | | | | | | | |
| Gao 2017b | 92 | 69.9 (18.1) | 46 | 71.5 (17.6) | | 84.15% | -0.09[-0.44,0.27] |
| **Subtotal ***** | **92** | | **46** | | | **84.15%** | **-0.09[-0.44,0.27]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.49(P=0.62) | | | | | | | |
| **Total ***** | **104** | | **58** | | | **100%** | **-0.16[-0.48,0.17]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.88, df=1(P=0.35); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=0.94(P=0.35) | | | | | | | |





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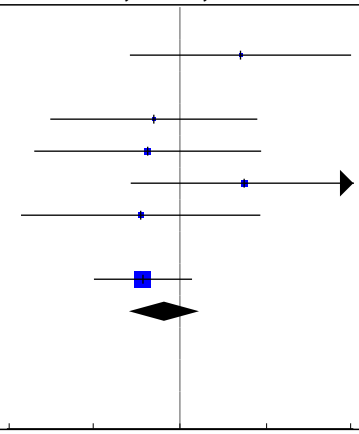
| Study or subgroup | Psychotherapy | | Usual care/ attention cont | | Std. Mean Difference | Weight | Std. Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | Random, 95% CI | | Random, 95% CI |
| Test for subgroup differences: Chi²=0.88, df=1 (P=0.35), I²=0% | | | | | | | |




Favours Psychotherapy — Favours Usual care/attention cont

## Analysis 3.17. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 17 Adverse events: death.

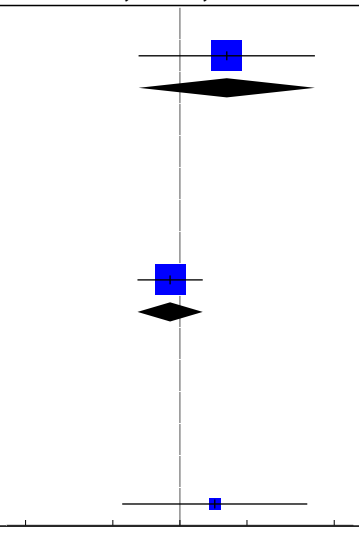
| Study or subgroup | Psychotherapy | Usual care/ attention cont | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H, Random, 95% CI | | M-H, Random, 95% CI |
| **3.17.1 At end of treatment** | | | | | |
| Alexopoulos 2012 | 2/12 | 0/12 | | 10.03% | 5[0.27,94.34] |
| Fang 2017 | 0/23 | 0/19 | | | Not estimable |
| Gao 2017b | 1/92 | 1/46 | | 11.45% | 0.5[0.03,7.81] |
| Lincoln 2003 | 0/39 | 2/84 | | 9.53% | 0.43[0.02,8.65] |
| Mitchell 2002 | 2/48 | 0/53 | | 9.54% | 5.51[0.27,111.97] |
| Thomas 2007 | 0/51 | 1/54 | | 8.57% | 0.35[0.01,8.46] |
| Towle 1989 | 0/21 | 0/23 | | | Not estimable |
| Watkins 2007 | 3/127 | 8/127 | | 50.89% | 0.38[0.1,1.38] |
| **Subtotal (95% CI)** | **413** | **418** | | **100%** | **0.65[0.26,1.66]** |
| Total events: 8 (Psychotherapy), 12 (Usual care/attention cont) | | | | | |
| Heterogeneity: Tau²=0; Chi²=4.8, df=5(P=0.44); I²=0% | | | | | |
| Test for overall effect: Z=0.9(P=0.37) | | | | | |




Favours Psychotherapy — Favours Usual care/attention cont

## Analysis 3.18. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 18 Adverse events: all.

| Study or subgroup | Psychotherapy | Usual care/ attention cont | Risk Ratio | Weight | Risk Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H, Random, 95% CI | | M-H, Random, 95% CI |
| **3.18.1 Recurrent stroke** | | | | | |
| Watkins 2007 | 2/127 | 0/127 | | 100% | 5[0.24,103.12] |
| **Subtotal (95% CI)** | **127** | **127** | | **100%** | **5[0.24,103.12]** |
| Total events: 2 (Psychotherapy), 0 (Usual care/attention cont) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.04(P=0.3) | | | | | |
| **3.18.2 Vascular events - not stroke (e.g. transient ischaemic attack)** | | | | | |
| Watkins 2007 | 5/127 | 7/127 | | 100% | 0.71[0.23,2.19] |
| **Subtotal (95% CI)** | **127** | **127** | | **100%** | **0.71[0.23,2.19]** |
| Total events: 5 (Psychotherapy), 7 (Usual care/attention cont) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.59(P=0.56) | | | | | |
| **3.18.3 Other events - not listed above (e.g. too ill)** | | | | | |
| Mitchell 2002 | 1/48 | 0/53 | | 35.75% | 3.31[0.14,79.28] |




Favours Psychotherapy — Favours Usual care/attention cont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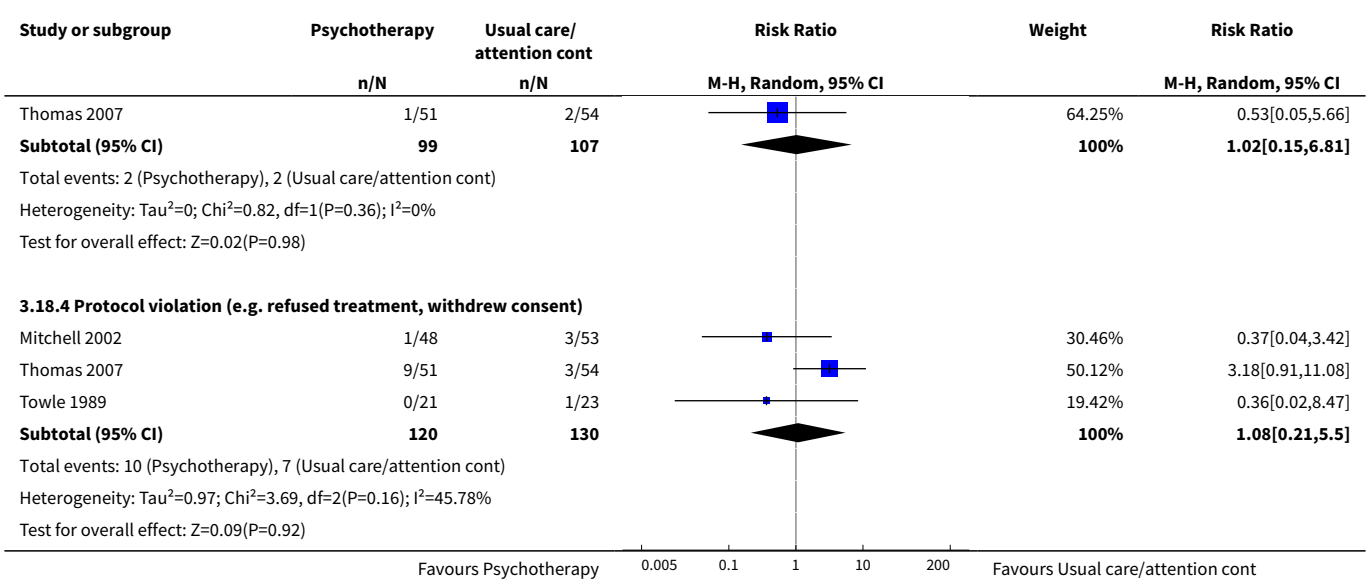
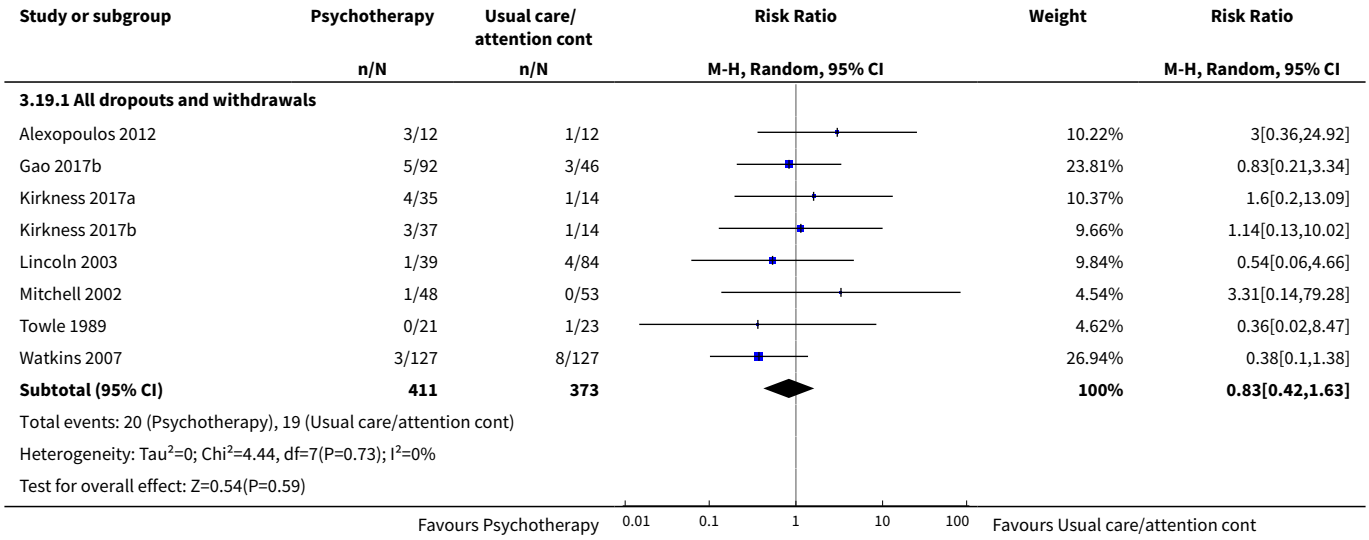



## Analysis 3.19. Comparison 3 Psychological therapy versus usual care and/or attention control, Outcome 19 Adverse events: leaving the study early (including death).




## Comparison 4. Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single)

| 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 | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |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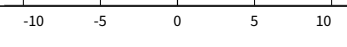
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2 Depression: < 50% reduction in scale scores at end of treatment | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Depression: mean scores at end of treatment | 2 | 198 | Mean Difference (IV, Fixed, 95% CI) | -1.53 [-2.10, -0.96] |
| 3.1 HDRS (high score = more depressed) | 2 | 198 | Mean Difference (IV, Fixed, 95% CI) | -1.53 [-2.10, -0.96] |
| 4 Anxiety: mean scores at end of treatment | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4.1 HAMA (high score = more anxious) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Activities of daily living: mean scores at end of treatment | 2 | 198 | Mean Difference (IV, Random, 95% CI) | 11.83 [0.27, 23.40] |
| 5.1 Barthel Index (high score = more dependent) | 2 | 198 | Mean Difference (IV, Random, 95% CI) | 11.83 [0.27, 23.40] |
| 6 Neurological function: mean scores at end of treatment | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6.1 Scandinavian Stroke Scale (low score = more neurological deficit) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Adverse events: death | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7.1 At end of treatment | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Adverse events: all | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.1 Gastrointestinal effects (e.g. constipation, diarrhoea) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Adverse events: leaving the study early (including death) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 9.1 All dropouts and withdrawals | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 4.3. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 3 Depression: mean scores at end of treatment.**

| Study or subgroup | Combination treatment | | Single treatment | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | Fixed, 95% CI | | Fixed, 95% CI |
| **4.3.1 HDRS (high score = more depressed)** | | | | | | | |
| Cao 2009a | 72 | 26.7 (5) | 72 | 30.2 (4.2) | | 14.22% | -3.5[-5.01,-1.99] |
| Wang 2005a | 27 | 8.9 (1.2) | 27 | 10.1 (1.1) | | 85.78% | -1.2[-1.81,-0.59] |





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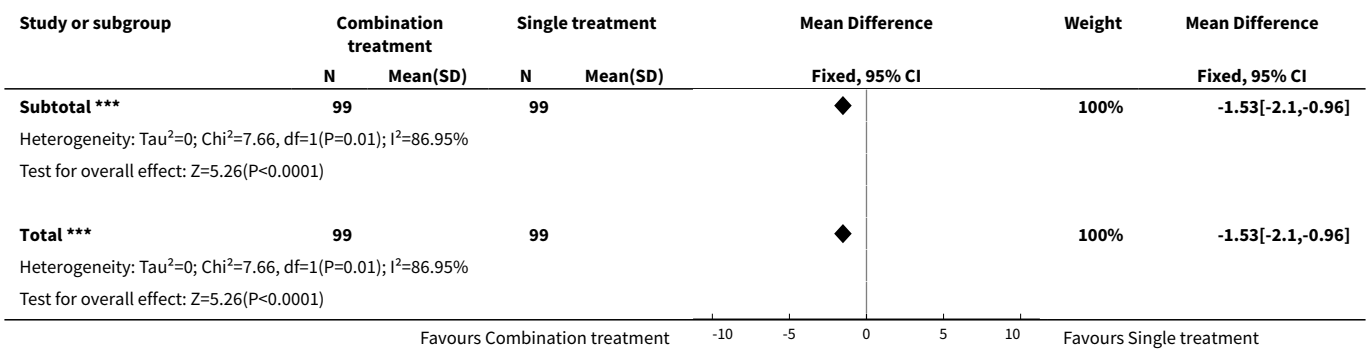
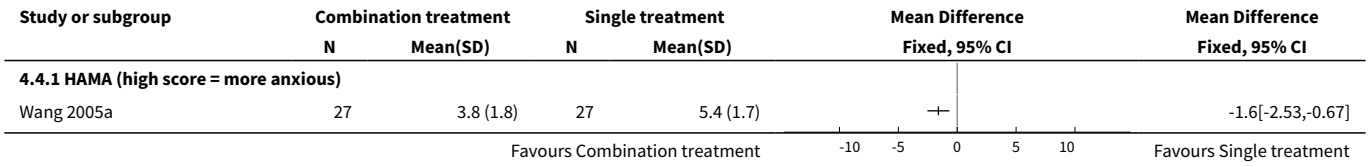
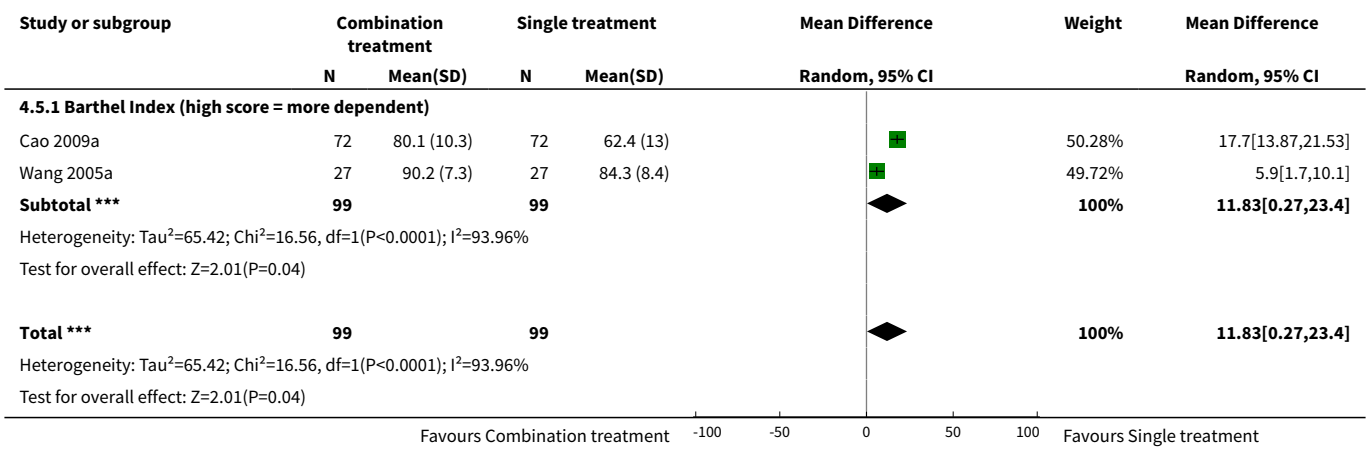



## Analysis 4.4. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 4 Anxiety: mean scores at end of treatment.




## Analysis 4.5. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 5 Activities of daily living: mean scores at end of treatment.





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### Analysis 4.6. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 6 Neurological function: mean scores at end of treatment.

| Study or subgroup | Combination treatment N | Combination treatment Mean(SD) | Single treatment N | Single treatment Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.6.1 Scandinavian Stroke Scale (low score = more neurological deficit)** | | | | | | |
| Wang 2005a | 27 | 5 (1.8) | 27 | 6.5 (1.6) | | -1.5[-2.41,-0.59] |




Favours Combination treatment — Favours Single treatment

### Analysis 4.7. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 7 Adverse events: death.

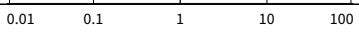
| Study or subgroup | Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **4.7.1 At end of treatment** | | | | |
| Wang 2005a | 0/27 | 0/27 | | Not estimable |




Favours Combination treatment — Favours Single treatment

### Analysis 4.8. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 8 Adverse events: all.

| Study or subgroup | Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **4.8.1 Gastrointestinal effects (e.g. constipation, diarrhoea)** | | | | |
| Wang 2005a | 10/27 | 9/27 | | 1.11[0.54,2.3] |




Favours Combination treatment — Favours Single treatment

### Analysis 4.9. Comparison 4 Pharmacological intervention and psychotherapy (combination) versus a pharmacological intervention and usual care or attention control (single), Outcome 9 Adverse events: leaving the study early (including death).

| Study or subgroup | Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **4.9.1 All dropouts and withdrawals** | | | | |
| Wang 2005a | 0/27 | 0/27 | | Not estimable |

Favours Combination treatment — Favours Single treatment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**Comparison 5. Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Depression: meeting the criteria for depression at end of treatment | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 1.1 HDRS (high score = more depressed) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Depression: < 50% reduction in scale scores at end of treatment | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1 HDRS | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Depression: mean scores at end of treatment | 9 | 685 | Mean Difference (IV, Random, 95% CI) | -4.09 [-5.61, -2.57] |
| 3.1 HDRS (high score = more depressed) | 9 | 685 | Mean Difference (IV, Random, 95% CI) | -4.09 [-5.61, -2.57] |
| 4 Depression: mean scores at end of follow-up | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4.1 HDRS (high score = more depressed) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Cognitive function: mean scores at end of treatment | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5.1 MMSE (low score = cognitive impairment) | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Activities of daily living: mean scores at end of treatment | 5 | 403 | Std. Mean Difference (IV, Random, 95% CI) | 2.03 [1.21, 2.85] |
| 6.1 Barthel Index (high score = more dependent) | 3 | 243 | Std. Mean Difference (IV, Random, 95% CI) | 2.49 [1.78, 3.19] |
| 6.2 ADL (high score = more impairment) | 2 | 160 | Std. Mean Difference (IV, Random, 95% CI) | 1.33 [-0.28, 2.94] |
| 7 Disability: mean scores at end of treatment | 2 | 180 | Mean Difference (IV, Random, 95% CI) | -10.02 [-20.14, 0.11] |
| 7.1 SDS (high score = more disability | 2 | 180 | Mean Difference (IV, Random, 95% CI) | -10.02 [-20.14, 0.11] |
| 8 Neurological function: mean scores at end of treatment | 4 | 280 | Mean Difference (IV, Random, 95% CI) | -2.78 [-4.13, -1.44] |
| 8.1 NIHSS (high score = more impairment) | 4 | 280 | Mean Difference (IV, Random, 95% CI) | -2.78 [-4.13, -1.44] |


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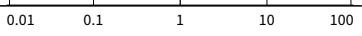
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9 Adverse events: death | 3 | 220 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.1 At end of treatment | 3 | 220 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Adverse events: all | 2 | 120 | Risk Ratio (M-H, Random, 95% CI) | 7.0 [0.38, 129.93] |
| 10.1 Other events - not listed above (e.g. insomnia, discomfort, headaches) | 2 | 120 | Risk Ratio (M-H, Random, 95% CI) | 7.0 [0.38, 129.93] |
| 11 Adverse events: leaving the study early (including death) | 4 | 300 | Risk Ratio (M-H, Random, 95% CI) | 1.33 [0.32, 5.58] |
| 11.1 All dropouts and withdrawals | 4 | 300 | Risk Ratio (M-H, Random, 95% CI) | 1.33 [0.32, 5.58] |

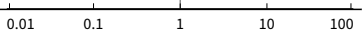
**Analysis 5.1. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 1 Depression: meeting the criteria for depression at end of treatment.**

| Study or subgroup | Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **5.1.1 HDRS (high score = more depressed)** | | | | |
| Du 2005 | 10/30 | 14/30 | | 0.71[0.38,1.35] |




**Analysis 5.2. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 2 Depression: < 50% reduction in scale scores at end of treatment.**

| Study or subgroup | Favours Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **5.2.1 HDRS** | | | | |
| Li 2013 | 26/30 | 21/30 | | 1.24[0.94,1.63] |





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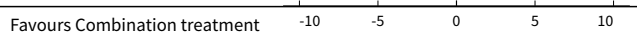
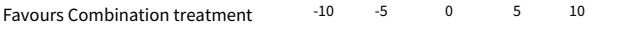
## Analysis 5.3. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 3 Depression: mean scores at end of treatment.

| Study or subgroup | Combination treatment N | Mean(SD) | Single treatment N | Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **5.3.1 HDRS (high score = more depressed)** | | | | | | | |
| Du 2005 | 30 | 6 (5) | 30 | 13 (7) | | 8.61% | -7[-10.08,-3.92] |
| Fan 2014 | 45 | 15.3 (2.4) | 45 | 16.7 (2.7) | | 12.53% | -1.39[-2.43,-0.35] |
| Jin 2013 | 30 | 14.1 (3.7) | 30 | 19.8 (2.9) | | 11.46% | -5.71[-7.38,-4.04] |
| Li 2013 | 30 | 13.3 (3.6) | 30 | 14.7 (3.9) | | 11.02% | -1.44[-3.34,0.46] |
| Li 2014 | 47 | 7.2 (3.6) | 46 | 11.2 (3.2) | | 12% | -4.04[-5.41,-2.67] |
| Liu 2015 | 30 | 13.5 (3.1) | 30 | 19.8 (2.8) | | 11.77% | -6.33[-7.83,-4.83] |
| Lu 2016 | 40 | 16.4 (7) | 40 | 24.5 (6.8) | | 8.7% | -8.05[-11.08,-5.02] |
| Sun 2013 | 50 | 19.8 (3.3) | 50 | 21.2 (3.3) | | 12.13% | -1.44[-2.74,-0.14] |
| Zhang 2013 | 41 | 9.5 (3.5) | 41 | 12.8 (3.5) | | 11.78% | -3.33[-4.83,-1.83] |
| **Subtotal ***** | **343** | | **342** | | | **100%** | **-4.09[-5.61,-2.57]** |
| Heterogeneity: $Tau^2$=4.53; $Chi^2$=64.31, df=8(P<0.0001); $I^2$=87.56% | | | | | | | |
| Test for overall effect: Z=5.26(P<0.0001) | | | | | | | |
| **Total ***** | **343** | | **342** | | | **100%** | **-4.09[-5.61,-2.57]** |
| Heterogeneity: $Tau^2$=4.53; $Chi^2$=64.31, df=8(P<0.0001); $I^2$=87.56% | | | | | | | |
| Test for overall effect: Z=5.26(P<0.0001) | | | | | | | |



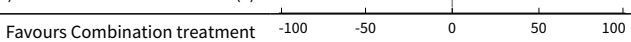

## Analysis 5.4. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 4 Depression: mean scores at end of follow-up.

| Study or subgroup | Combination treatment N | Mean(SD) | Single treatment N | Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.4.1 HDRS (high score = more depressed)** | | | | | | |
| Jiang 2014b | 50 | 5 (0.8) | 50 | 8 (1.2) | + | -3[-3.4,-2.6] |




## Analysis 5.5. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 5 Cognitive function: mean scores at end of treatment.

| Study or subgroup | Combination treatment N | Mean(SD) | Single treatment N | Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.5.1 MMSE (low score = cognitive impairment)** | | | | | | |
| Du 2005 | 30 | 24 (7) | 30 | 18 (6) | + | 6[2.7,9.3] |





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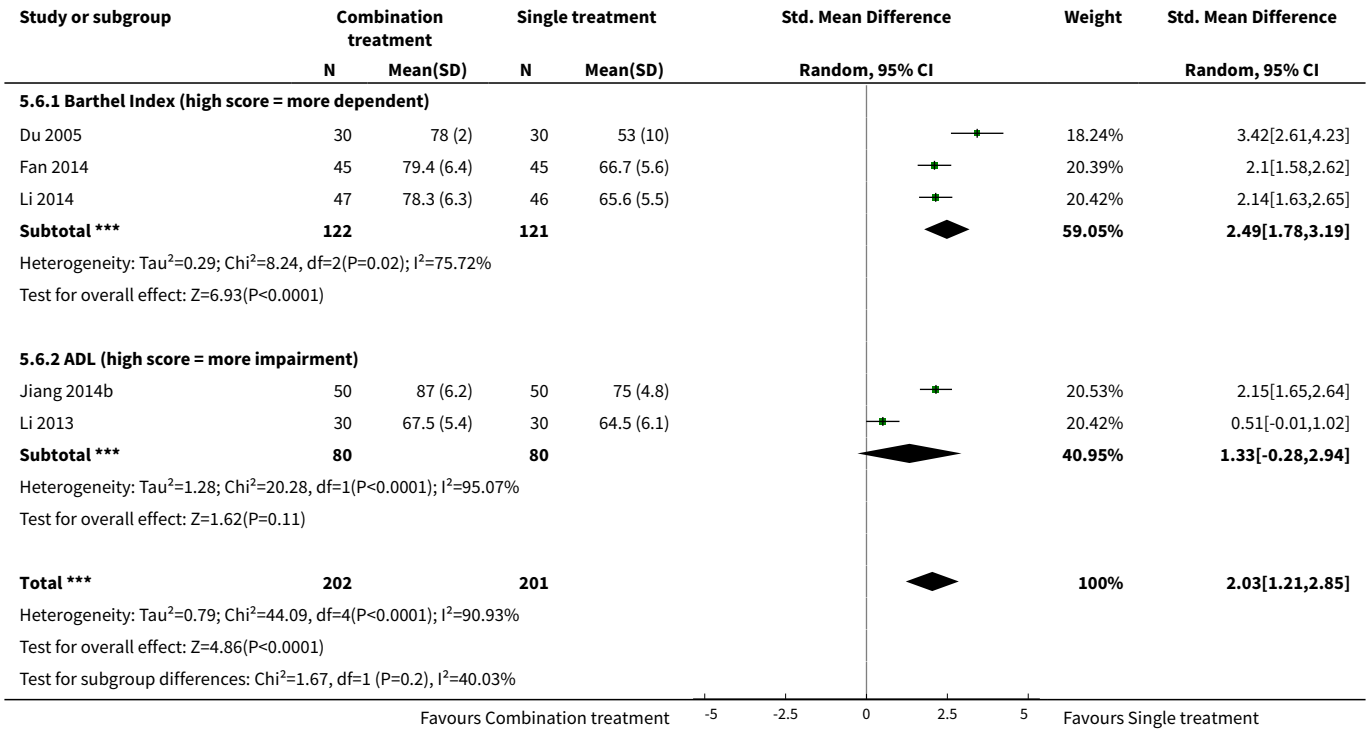
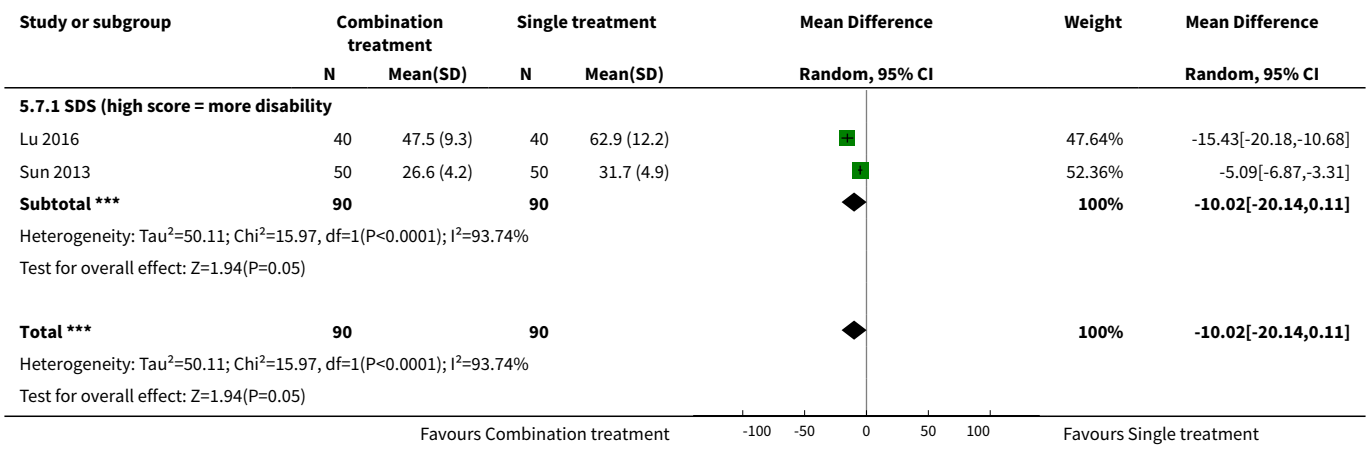
## Analysis 5.6. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 6 Activities of daily living: mean scores at end of treatment.




## Analysis 5.7. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 7 Disability: mean scores at end of treatment.





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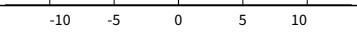
## Analysis 5.8. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 8 Neurological function: mean scores at end of treatment.

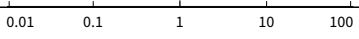
| Study or subgroup | Combination treatment N | Mean(SD) | Single treatment N | Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **5.8.1 NIHSS (high score = more impairment)** | | | | | | | |
| Jiang 2014b | 50 | 5 (0.9) | 50 | 9 (1.5) | | 30.48% | -4[-4.48,-3.52] |
| Jin 2013 | 30 | 6.1 (2.1) | 30 | 8.6 (3.1) | | 24.09% | -2.54[-3.89,-1.19] |
| Li 2013 | 30 | 10.3 (2.5) | 30 | 11.5 (3.1) | | 23.55% | -1.18[-2.59,0.23] |
| Liu 2015 | 30 | 6.1 (3) | 30 | 9.2 (3.3) | | 21.88% | -3.08[-4.68,-1.48] |
| **Subtotal ***** | **140** | | **140** | | | **100%** | **-2.78[-4.13,-1.44]** |
| Heterogeneity: $Tau^2$=1.48; $Chi^2$=16.68, df=3(P=0); $I^2$=82.02% | | | | | | | |
| Test for overall effect: Z=4.05(P<0.0001) | | | | | | | |
| **Total ***** | **140** | | **140** | | | **100%** | **-2.78[-4.13,-1.44]** |
| Heterogeneity: $Tau^2$=1.48; $Chi^2$=16.68, df=3(P=0); $I^2$=82.02% | | | | | | | |
| Test for overall effect: Z=4.05(P<0.0001) | | | | | | | |




Favours Combination treatment — Favours Single treatment

## Analysis 5.9. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 9 Adverse events: death.

| Study or subgroup | Combination treatment n/N | Single treatment n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **5.9.1 At end of treatment** | | | | | |
| Du 2005 | 0/30 | 0/30 | | | Not estimable |
| Jiang 2014b | 0/50 | 0/50 | | | Not estimable |
| Liu 2015 | 0/30 | 0/30 | | | Not estimable |
| **Subtotal (95% CI)** | **110** | **110** | | | **Not estimable** |
| Total events: 0 (Combination treatment), 0 (Single treatment) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **Total (95% CI)** | **110** | **110** | | | **Not estimable** |
| Total events: 0 (Combination treatment), 0 (Single treatment) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |




Favours Combination treatment — Favours Single treatment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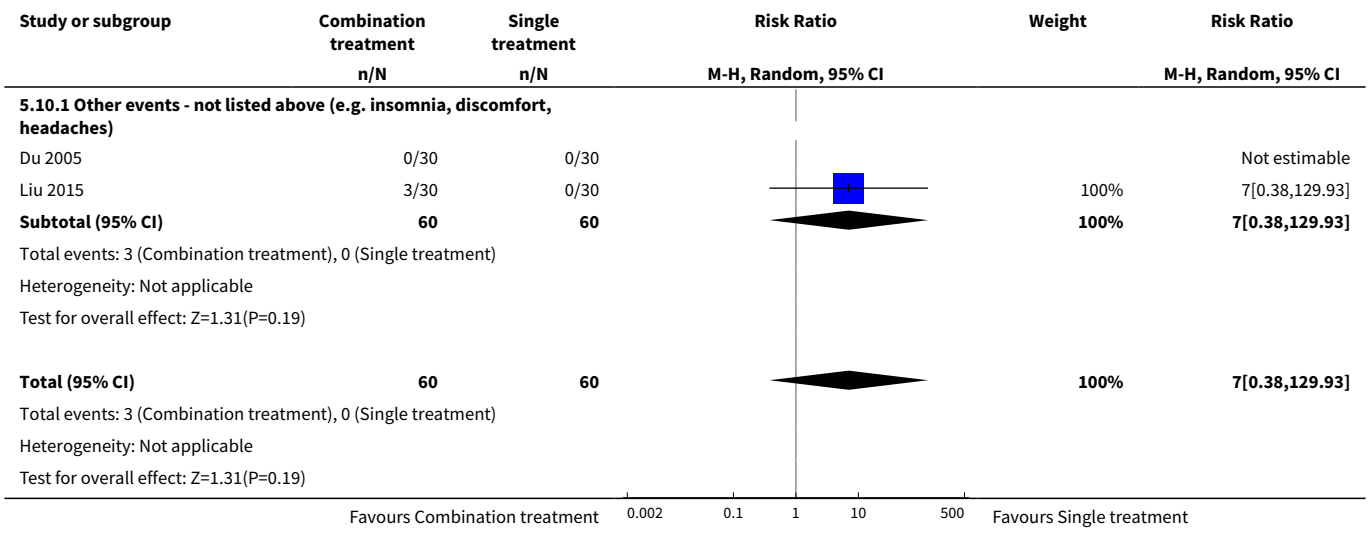
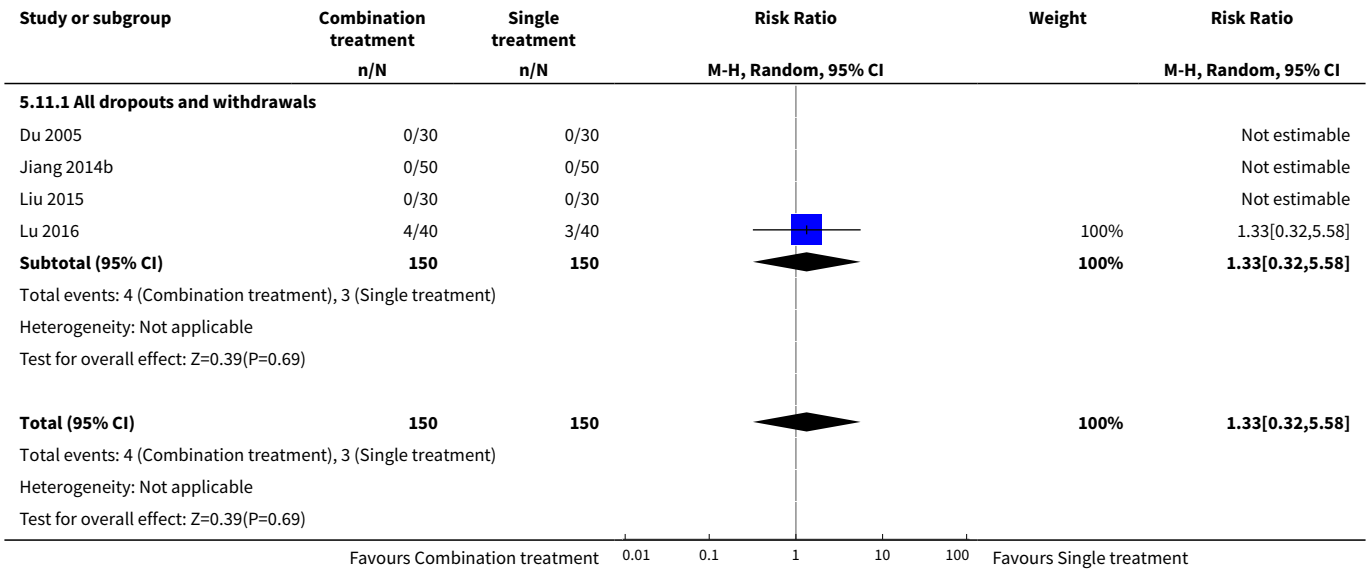
**Analysis 5.10. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 10 Adverse events: all.**




**Analysis 5.11. Comparison 5 Non-invasive brain stimulation and a pharmacological intervention (combination) versus a pharmacological intervention and sham stimulation or usual care (single), Outcome 11 Adverse events: leaving the study early (including death).**




## ADDITIONAL TABLES

**Table 1. Characteristics of 'dropout' studies**

| Study ID | Methods | Participants | Interventions | Out-comes | Notes |
|---|---|---|---|---|---|


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| Bramanti 1989 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** protirelin tartrate (TRH-T)<br>**Control arm:** placebo | **Geographical location:** Italy<br>**Setting:** unclear<br>**Number of participants:** 30<br>**Stroke criteria:** acute stroke<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** not reported<br>**Depression criteria:** not reported<br>**Total number included in this trial:** unclear (63% men, mean age 72.2, SD not reported for the overall cohort)<br>**Number included in treatment group:** unclear<br>**Number included in control group:** unclear | **Treatment:** protirelin tartrate (TRH-T) 2 mg/d<br>**Control:** placebo<br>**Duration:** 2 weeks<br>**Follow-up:** none | • Depression measured using HDRS | Results not available in format suitable for this review |
| Chang 2011 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** rational emotive behaviour therapy (REBT) + usual care<br>**Control arm:** usual care | **Geographical location:** China<br>**Setting:** inpatient<br>**Number of participants:** 16<br>**Stroke criteria:** ischaemic strokes<br>**Method of stroke diagnosis:** diagnosis confirmed by imaging<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** (1) history of mental illness; (2) cognitive impairment; (3) severe aphasia; (4) > 2 weeks post stroke<br>**Depression criteria:** Chinese version of HDRS score ≥ 35<br>**Total number included in this trial:** 16 (% men and age unknown)<br>**Number included in treatment group:** 8<br>**Number included in control group:** 8 | **Treatment:** REBT + usual care. REBT counselling therapy (1 to 2 hour sessions/week) consisting of a knowledge component (education about health psychology and recovery from hemiplegic stroke) and a behavioural training component (belief changes, forgiveness training, anger management)<br>**Administered by:** a trained psychology graduate (regular care administered by hospital nurses)<br>**Supervision:** unclear<br>**Intervention fidelity:** not reported<br>**Control:** usual care<br>**Duration:** 1 month | • Depression measured using Chinese version of HDRS<br>• Anxiety measured using Chinese version of HARS<br>• Disability measured using Chinese version of BI | Unable to isolate outcome data for those with depression at randomisation |
| Choi-Kwon 2006 | **Study design:** parallel design | **Geographical location:** South Korea<br>**Setting:** outpatients<br>**Number of participants:** 152<br>**Stroke criteria:** ischaemic stroke | **Treatment:** fluoxetine (SSRI) 20 mg daily<br>**Control:** matched placebo<br>**Duration:** 3 months | • Depression measured | Unable to isolate outcome data for those with |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | **Number of arms:** 2<br><br>**Experimental arm:** fluoxetine (SSRI)<br><br>**Control arm:** matched placebo | **Method of stroke diagnosis:** diagnosis via CT and MRI scans; interview performed on average of 14 months after stroke<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) did not undergo imaging (CT/MRI) studies; (2) SAH; (3) had TIA without progression to stroke; (4) severe communication problems (aphasia, dementia, or dysarthria); (5) scored < 23 on MMSE; (6) history of depression or psychiatric illness before onset of stroke; (7) already treated with psychiatric regimens; (8) lived alone<br><br>**Depression criteria:** psychiatric interview, BDI score > 13<br><br>**Total number included in this trial:** 152<br><br>**Number included in treatment group:** 76 (75% men, mean age 58 years, SD 9)<br>**Number included in control group:** 76 (79% men, mean age 58 years, SD 9) | | • using BDI<br>• Leaving the study early<br>• Adverse events | depression at randomisation |
| Delbari 2011 | **Study design:** parallel design<br>**Number of arms:** 4<br><br>**Experimental arm A:** methylphenidate + placebo<br><br>**Experimental arm B:** levodopa + placebo<br><br>**Experimental arm C:** methylphenidate + levodopa<br><br>**Control arm:** 2 × 10 mg placebo + 1 × 125 | **Geographical location:** Iran<br><br>**Setting:** inpatient<br>**Number of participants:** 78<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) only patients with limb (arm or leg) paresis<br><br>**Exclusion criteria:** (1) unable to respond or directly consent; (2) comorbidities requiring strict blood pressure control and put at risk by the potential of hypertension from MPH therapy (history of haemorrhagic stroke, recent myocardial infarction within 4-week period, decompensated cardiac insufficiency, tachycardia, uncontrolled hypertension, unstable metabolic disease, glaucoma); (3) potential for adverse outcomes from stimulant effects of MPH, including seizure and agitation major cognitive deficits preventing adequate study participation; (4) currently taking alpha-adrenergic agonists, antagonists, neuroleptics, benzodiazepines, MAO inhibitors, or antidepressants; (5) known hypersensitivity to MPH or LD | **Treatment A:** 2 × 10 mg methylphenidate + 125 mg placebo (content unknown)<br><br>**Treatment B:** 1 × 12.5 mg levodopa + 2 × 10 mg placebo<br><br>**Treatment C:** 2 × 10 mg methylphenidate + 1 × 125 mg levodopa<br><br>**Control:** 2 × 10 mg placebo + 1 × 125 mg placebo<br><br>**Duration:** 5 days a week for a total of 15 sessions | • Depression measured using GDS<br>• Cognitive function measured using MMSE | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | mg placebo | **Depression criteria:** GDS < 7.8<br><br>**Total number included in this trial:** 78<br><br>**Number included in Treatment A:** 19 (47% men, mean age 64.05, SD 10.8)<br><br>**Number included in Treatment B:** 20 (70% men, mean age 66.3, SD 9.5)<br><br>**Number included in Treatment C:** 19 (58% men, 60.2, SD 9.1)<br><br>**Number included in control group:** 20 (70% men, mean age 65.3, SD 9.6) | | | |
| Downes 1995 | **Study design:** parallel design<br><br>**Number of arms:** 3<br><br>**Experimental arm 1:** information + counselling<br><br>**Experimental arm 2:** information pack<br><br>**Control arm:** standard care | **Geographical location:** UK<br>**Setting:** outpatient<br>**Number of participants:** 62<br><br>**Stroke criteria:** not reported<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) lived at home; (2) had an informal carer; (3) stroke increase in mRS; (4) poststroke mRS score of 2 to 5<br><br>**Exclusion criteria:** (1) not living at home; (2) not having an informal carer; (3) having no increase in disability or change in lifestyle/dependency<br><br>**Total number included in this trial:** 62<br><br>**Number included in treatment 1:** 22 (50% men, age not reported)<br>**Number included in treatment 2:** 22 (55% men, age not reported)<br>**Number included in control group:** 18 (44% men, age not reported) | **Treatment 1:** information plus counselling. Egan's problem-solving approach, individual is helped to explore concerns, clarify problems, set goals, and take appropriate action. Protocol discussed first and formulated into a counsellor/client contract. Information pack containing information on physical, cognitive, behavioural, and emotional effects of stroke, carer well-being, and local services<br>**Treatment 2:** information only: information pack containing information on physical, cognitive, behavioural, and emotional effects of stroke, carer well-being, and local services<br>**Control:** standard care, no visit(s) or information pack provided<br>**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<br>**Delivered by:** nurse counsellor | • Depression measured using HADS-Depression<br>• Anxiety measured using HADS-Anxiety | Unable to isolate outcome data for those with depression at randomisation |
| Hadidi 2014 | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** problem-solving therapy (PST)<br><br>**Control arm:** | **Geographical location:** USA<br><br>**Setting:** inpatient<br>**Number of participants:**<br><br>**Stroke criteria:** first-time diagnosis of ischaemic stroke < 48 hours<br><br>**Method of stroke diagnosis:** not reported<br><br>**Inclusion criteria:** (1) Mini-Cog score of 3; ≥ 50 years of age; (2) able to read and write in English<br><br>**Exclusion criteria:** (1) previous history of mental health problems; (2) diagnosis of severe aphasia as identified by | **Treatment:** 1-on-1 problem-solving therapy sessions lasting 1 to 2 hours. Therapy entails providing patient information on impact and guidance to enable the patient to identify and define the problem; brainstorm all potential solutions; select the most appropriate and feasible solution; create and implement a SMART (Specific, Measureable, Achievable, Realistic, and Timely) goal; evaluate and review progress in follow-up sessions<br><br>**Administered by:** a doctoral nursing student who received PST training through a 13-module online pro- | • Depression measured using CES-D<br>• Impairment measured using FIM<br>• Leaving the | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | weekly telephone calls | a speech pathologist; (3) haemorrhagic stroke or transient ischaemic attack; (4) medical instability requiring transfer to critical care<br><br>**Depression criteria:** CES-D score measured at baseline but patients recruited regardless of their CES-D score. If CES-D score > 10, or suicidal ideation, the primary physician was notified<br><br>**Total number included in this trial:** 22<br><br>**Number included in treatment group:** 11 (18% men, mean age 73)<br><br>**Number included in control group:** 11 (45% men, mean age 69) | gram adapted from standard 3-day in-person training<br><br>**Supervision:** principal Investigator who had undergone in-person PST training<br><br>**Intervention fidelity:** not reported<br><br>**Control:** weekly telephone calls to assess CES-D and FIM scores<br><br>**Duration:** once per week for 10 weeks | | trial early |
| Jorge 2004 | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** rTMS<br><br>**Control arm:** sham rTMS | **Geographical location:** USA<br>**Setting:** outpatient<br>**Number of participants:** 20<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** clinical diagnosis of ischaemic stroke confirmed by imaging<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) haemorrhagic stroke; (2) clinical evidence of dementia MMSE scores < 23; (3) aphasia with severe language comprehension deficits; (4) alcohol or drug abuse during past 12 months; (5) severe systemic disease or ongoing neoplasia; (6) neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease; (7) contraindications to rTMS including prior occurrence of induced seizures; major head trauma; or history of idiopathic epilepsy; presence of metal in the skull, cranial cavity, or brain parenchyma; cardiac pacemaker, implanted defibrillator, or intracardiac lines<br><br>**Depression criteria:** psychiatric diagnosis (i.e. depression due to stroke with major depressive-like episode or research criteria for minor depression) was made using symptoms elicited by a version of the Present State Examination modified to identify DSM-IV symptoms of depression and anxiety disorder; evidence that depression was unresponsive to at least 2 treatments with antidepressants given in adequate doses; clear clinical indication | **Treatment:** rTMS delivered over the left pre-frontal cortex at frequency of 10 Hz, intensity of 110% of the motor threshold, duration of 5 seconds, and total of 20 trains separated by 60-second pauses. Cumulative rTMS exposure for the 10-Hz stimuli was 5 seconds × 20 per session × 10 sessions × 1000 seconds of cumulative exposure or a total of 10,000 magnetic pulses<br><br>**Control:** sham stimulation: similar stimulation parameters to the rTMS stated but with the coil angled off the head, to produce a 67% to 73% reduction in the magnetic field<br><br>**Administered by:** investigators at the ECT facility in the Department of Psychiatry<br><br>**Duration:** 2 weeks | • Depression clinical response (reduction in HDRS total score ≥ 50% and patient no longer meeting DSM-IV criteria for depression diagnosis)<br>• Remission of depression (reduction in HDRS total score ≥ 50% with final HDRS score < 8) | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | of a significant change in the course or severity of depressive disorder after stroke<br><br>**Total number included in this trial:** 20<br><br>**Number included in treatment group:** 10 (60% men; mean age 63.1, SD 8.1)<br><br>**Number included in control group:** 10 (50% men; mean age 66.5, SD 12.2) | | • Depression measured using 17-item HDRS<br>• Cognitive function measured using MMSE<br>• Adverse events | |
| Jorge 2008 | **Study design:** parallel design<br>**Number of arms:** 4<br><br>**Experimental arm A:** 10 rTMS sessions<br><br>**Experimental Arm B:** 15 rTMS sessions<br><br>**Control arm A:** 10 sham rTMS<br><br>**Control arm B:** 15 sham rTMS | **Geographical location:** USA<br><br>**Setting:** mixed<br>**Number of participants:** unclear<br><br>**Stroke criteria:** not an entry criteria. Includes patients with clinical diagnosis of vascular depression<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) presence of severe heart or respiratory failure or renal or hepatic failure, or occurrence of ongoing neoplastic process; (2) neurodegenerative disorders such as idiopathic Parkinson's disease or probable Alzheimer's disease and clinical evidence of dementia (Clinical Dementia Rating Scale score 0.5); (3) depressed patients who were actively suicidal, who presented with prominent psychotic features, or with comorbid alcohol or other drug abuse that was active within 2 years before the study; (4) prior occurrence of induced seizures, major head trauma, and history of epilepsy; (5) metal in the skull, cranial cavity, or brain parenchyma; cardiac pacemaker, implanted defibrillator, or medication pump<br><br>**Depression criteria:** diagnosis of major depression during current depressive episode<br><br>**Total number included in this trial:** number of stroke patients unclear | **Treatment A:** 10 rTMS sessions in the left DLPFC at frequency of 10 Hz and intensity of 110% of the motor threshold during a 6-second period, with a total of 20 trains separated by 1-minute pauses. Treatment was administered during a 10-day period for a TCD of 12,000 pulses (i.e. TCD-12K group)<br><br>**Treatment B:** 15 rTMS sessions in the left pre-frontal cortex at frequency of 10 Hz and intensity of 110% of the motor threshold during a 6-second period, with a total of 20 trains separated by 1-minute pauses. Treatment was administered during a 10-day period with 2 sessions per day for 5 days to achieve a TCD of 18,000 pulses (i.e. TCD-18K group)<br><br>**Control A:** 10 sham stimulation sessions with matched pulses but performed with a specially designed coil that looks exactly like the standard stimulating coil but produces scalp sensation without actual cortical stimulation<br><br>**Control B:** 15 sham stimulation sessions<br><br>**Duration:** 10 days | • Depression - unclear what measure was used | Unable to obtain information about whether any participants in this study have a diagnosis of stroke and whether some participants who received treatment A are the same as those reported in Jorge 2004 |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
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| | | **Number included in treatment group:** number of stroke patients unclear<br><br>**Number included in control group:** number of stroke patients unclear | | | |
| Kim 2017 | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** escitalopram<br><br>**Control arm:** placebo | **Geographical location:** South Korea<br><br>**Setting:** unclear<br><br>**Number of participants:** 478<br><br>**Stroke criteria:** ischaemic stroke or intracerebral haemorrhage<br><br>**Method of diagnosis:** diagnosis confirmed by MRI or CT<br><br>**Inclusion criteria:** (1) acute ischaemic stroke or intracerebral haemorrhage within previous 21 days<br><br>**Exclusion criteria:** (1) history of diagnosed depression or other psychiatric diseases before index stroke; (2) severe dementia, defined as requiring assistance from others to maintain activities of daily living because of cognitive dysfunction (stages 5 to 7 of the Global Deterioration Scale); (3) aphasia resulting in communication difficulties regardless of reasons; (4) exhibiting strong suicidal thoughts (combined MADRS score > 8 on ninth and tenth questions); (5) seizures; (6) history of other brain disease or head trauma within 30 days before screening; (7) abnormal blood tests such as abnormal liver function test or renal insufficiency; (8) pregnant or lactating<br><br>**Depression criteria:** none<br><br>**Total number included in this trial:** 478<br><br>**Number included in treatment group:** 241 (57% men, mean age 63.6, SD 12.6)<br><br>**Number included in control group:** 237 (65% men, mean age 63.5, SD 12.0) | **Treatment:** escitalopram (5 mg daily as a starting dose, dose increased to 10 mg daily from the second week and then every other day for 1 week)<br><br>**Control:** placebo<br><br>**Duration:** 12 weeks<br><br>**Follow-up:** 6 months | • Depression measured using MADRS<br>• Emotional incontinence measured using Kim's criteria<br>• Anger proneness measured using Spielberg Train Anger Scale<br>• Impairment measured using NIHSS<br>• Disability measured using mRS and BI | Unable to isolate outcome data for those with depression at randomisation |
| Kim 2017a | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental** | **Georgraphical location:** South Korea<br>**Setting:** inpatient<br>**Number of participants:** 44<br>**Stroke criteria:** right hemisphere ischaemic or haemorrhagic stroke<br><br>**Method of stroke diagnosis:** unclear | **Treatment:** rTMS. rTMS stimulus was targeted at P3, over the left parieto-occipital cortex, and at P4, over the right parieto-occipital cortex. To set the motor threshold before stimulation, a cotton cap with a grid ($1 \times 1$ cm$^2$) was fixed to the scalp from the nasion to the inion, a magnetic stimulus was applied to | • Depression measured using BD<br>• Activities of | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
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| | **arm:** rTMS<br>**Control arm:** sham rTMS | **Inclusion criteria:** (1) diagnosis of right hemisphere ischaemic or haemorrhagic stroke<br>**Exclusion criteria:** (1) severe cognitive impairment that made it difficult to understand instructions; (2) seizures; (3) severe head trauma; (4) metal skull implant; (5) pacemaker<br>**Depression criteria:** none<br>**Total number included in this trial:** 44<br>**Number included in treatment group:** 22 (82% men, mean age 52.6, SD 10.6)<br>**Number included in control group:** 22 (59% men, mean age 64.3, SD 11.5) | the cranium, and motor-evoked potentials were measured. Low-frequency rTMS stimulation was applied to P3 on the left, healthy side, using a 1-Hz stimulus at 90% motor threshold, 4 times, for 5 minutes at a time, separated by 1-minute intervals. High-frequency rTMS was applied to P4 on the right, affected side, using a 5-Hz stimulus at 90% motor threshold, 20 times, for 5 seconds at a time, separated by 55-second intervals<br>**Control:** sham rTMS. Mock stimulus used the same protocol as low-frequency rTMS, except that the coil was not placed against the skull, and the stimulus was applied in the vertical direction<br>**Duration:** 12 weeks<br>**Follow-up:** 8 weeks | daily living measured using FIM | |
| Kootker 2012 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** tailored cognitive-behavioural therapy (CBT)<br>**Control arm:** computer cognitive training (CCT) | **Geographical location:** The Netherlands<br>**Setting:** outpatient<br>**Number of participants:** 61<br>**Stroke criteria:** all subtypes<br>**Method of stroke diagnosis:** clinically confirmed stroke<br>**Inclusion criteria:** (1) sustained any type of clinically confirmed stroke at least 3 months earlier; (2) only mild cognitive impairment (MMSE score); (3) scoring positively on communication-related items of NIHSS; (4) master Dutch language<br>**Exclusion criteria:** (1) pre-stroke major depression requiring psychiatric care; (2) poststroke major depression requiring a start with medication; (3) pre-morbid disability as reflected in a BI score < 19 (out of 20); (4) severe comorbidity that might affect mood (e.g. cancer)<br>**Depression criteria:** HADS score > 7<br>**Total number included in this trial:** 61<br>**Number included in treatment group:** 31 (61.3% men, mean age 61, SD not reported) | **Treatment:** tailored cognitive-behavioural therapy. Each session consisted of 2 × 20 to 25-minute blocks divided by a 10 to 15-minute break. Therefore, each session lasted approximately 1 hour. Goals for attaining daily life activities were primarily set together by the patient and the therapist using pictures from the Activity Card Sort. Concurrently with psychological sessions, the CBT intervention was augmented with 3 sessions of occupational therapy or movement therapy. During these sessions, an occupational or movement therapist helped patients in establishing and attaining goals aimed at meaningful activities and social participation. These goals were attuned to the content of the psychological sessions<br>**Administered by:** certified healthcare psychologist (therapist)<br>**Supervision:** not reported<br>**Intervention fidelity:** not reported<br>**Control:** computer cognitive training. A desktop was set up with headphones and a keyboard with coloured patches attached to 2 keys. Patients could select any (or a combination) of 4 specific cognitive domains for training (i.e. attention, memory, executive functioning, visual attention). As patients | • Depression measured using HADS-Depression<br>• Anxiety measured using HADS-Anxiety<br>• Quality of life measured using EQ5D | Results not available in format suitable for this review |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
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| | | **Number included in control group:** 30 (63.3%, mean age 61, SD not reported) | improved, the Cogniplus Program adjusted the level of difficulty for each training task accordingly. In this way, each patient trained at his/her individual level and pace<br><br>**Administered by:** self-administered, but cognitive trainers or psychological assistants were present to assist participants during training<br><br>**Duration:** 4 months<br><br>**Follow-up:** 12 months | | |
| Mauri 1988 | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:**<br>mianserin<br><br>**Control arm:** placebo | **Geographical location:** Spain<br>**Setting:** unclear<br><br>**Number of participants:** unclear<br>**Stroke criteria:** ischaemic stroke<br><br>**Method of diagnosis:** unclear<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** not reported<br><br>**Depression criteria:** GDS (15 item) score > 4<br><br>**Total number included in this trial:** unclear<br><br>**Number included in treatment group:** unclear<br>**Number included in control group:** unclear | **Treatment:** mianserin<br>**Control:** placebo<br>**Duration:** 6 weeks | • Depression - unclear what measure was used | Results not available in format suitable for this review |
| Meara 1998 | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** sertraline<br><br>**Control arm:** placebo | **Geographical location:** UK<br>**Setting:** inpatient<br>**Number of participants:** unclear<br><br>**Stroke criteria:** ischaemic stroke<br><br>**Method of stroke diagnosis:** unclear<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) moderate to severe dementia; (2) severe aphasia, communication difficulties; (3) poorly controlled epilepsy<br><br>**Depression criteria:** GDS (15 item) score > 4<br><br>**Total number included in this trial:** unclear<br><br>**Number included in treatment:** unclear<br>**Number included in control group:** unclear | **Treatment:** sertraline, 50 mg daily. Dose escalation to 100 mg for non-responders at 2 weeks<br>**Control:** matched placebo<br>**Duration:** 6 weeks | • Depression measured using GDS | Results not available in format suitable for this review |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| Ohtomo 1985 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** tiapride<br>**Control arm:** placebo | **Geographical location:** Japan<br>**Setting:** unclear<br>**Number of participants:** 188<br>**Stroke criteria:** all subtypes<br>**Method of stroke diagnosis:** diagnosis via clinical signs and CT<br>**Inclusion criteria:** (1) > 40 years of age, high blood pressure (> 160/90 mmHg), and hypertensive changes on fundoscopy changes; (2) stable neuroleptic, minor tranquilliser, antidepressant, brain metabolic activators, cerebro-vasodilators washed out for 3 to 7 days before randomisation<br>**Exclusion criteria:** (1) severe aphasia; (2) severe dementia; (3) drug dependence; (4) inadequate conditions for the study<br>**Depression criteria:** not reported<br>**Total number included in this trial:** 288<br>**Number included in treatment group:** 141 (54% men, mean age not reported)<br>**Number included in control group:** 147 (61% men, mean age not reported) | **Treatment:** tiapride, 75 mg daily for 1 week, dose escalation to 150 to 225 mg daily for 5 weeks according to clinical response<br>**Control:** matched placebo<br>**Duration:** 6 weeks | • Depression - unclear what measure was used | Unable to isolate outcome data for those with depression at randomisation |
| Ostwald 2014 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** counselling + mailed information<br>**Control arm:** mailed information | **Geographical location:** USA<br>**Setting:** outpatient<br>**Number of participants:** 159<br>**Stroke criteria:** not reported<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** (1) history of psychopathology for patient or caregiver; (2) globally aphasic preventing communication and consent; (3) patient or caregiver has comorbidity that would take priority over stroke rehabilitation; (4) life expectancy < 6 months<br>**Depression criteria:** depression not an entry criterion<br>**Total number included in this trial:** 159<br>**Number included in treatment group:** 80 (69% men, mean age 66.98, SD 9.04) | **Treatment:** home visits from a multi-disciplinary therapy team to provide education, support, skill training, counselling, and linkages to social and community resources + mailed information. Average dose 36.7 hours<br>**Administered by:** advanced practice nurses, occupational and physical therapists<br>**Supervision:** not reported<br>**Intervention fidelity:** not reported<br>**Control:** mailed information<br>**Duration:** 6 months | • Depression measured using GDS<br>• Disability measured using FIM<br>• Quality of life measured using SF-36 | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | **Number included in control group:** 79 (81% men, mean age 65.75, SD 9.26) | | | |
| Raffaele 1996 | **Study design:** parallel design<br>**Number of arms:** 2<br>**Experimental arm:** trazodone<br>**Control arm:** placebo | **Geographical location:** Italy<br>**Setting:** outpatient<br>**Number of participants:** 22<br>**Stroke criteria:** unclear<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** not reported<br>**Exclusion criteria:** not reported<br>**Depression criteria:** ZDS<br>**Total number included in this trial:** 22<br>**Number included in treatment group:** 11 (45.4% men, mean age 69.5, SD 2.3)<br>**Number included in control group:** 11 (72.7% men, mean age 70.4, SD 3.0) | **Treatment:** trazodone 300 mg/d<br>**Control:** placebo<br>**Duration:** 30 to 45 days<br>**Follow-up:** unclear | • Depression measured using ZDS<br>• Activities of daily living measured using BI | Unable to isolate outcome data for those with depression at randomisation |
| Robinson 2000 | **Study design:** cross-over design<br>**Number of arms:** 3<br>**Experimental arm 1:** nortriptyline<br>**Experimental arm 2:** fluoxetine<br>**Control arm:** placebo | **Geographical location:** USA<br>**Setting:** mixed<br>**Number of participants:**<br>**Stroke criteria:** infarction and haemorrhage<br>**Method of stroke diagnosis:** not reported<br>**Inclusion criteria:** (1) acute stroke within 6 months of onset of the study; (2) taking antidepressants other than fluoxetine at the time of enrolment and allowed to stop antidepressants for a 2-week washout period before the study; (3) patient's immediate family and treating physician agree to the patient's participation<br>**Exclusion criteria:** (1) severe comprehension<br>deficit that precluded a verbal interview (defined as failing part 1 of the Token Test); (2) any other significant medical illness that would threaten life or recovery from stroke; (3) prior history of head injury; (4) prior history of other brain disease with the exception of prior stroke | **Treatment 1:** nortriptyline (SNRI). Doses of 25 mg/d gradually increased to 100 mg/d<br>**Treatment 2:** fluoxetine (SSRI). Doses of 10 mg/d gradually increased to 40 mg/d<br>**Control:** matched placebo<br>**Duration:** 12 weeks<br>**Follow-up:** none | • Depression measured using 24-item HDRS<br>• Anxiety measured using HARS<br>• Activities of daily living measured using FIM and John Hopkins Functional Inventory<br>• Cognitive | Unable to isolate outcome data for those with depression at randomisation |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | **Depression criteria:** DSM-IV and HDRS<br><br>**Total number included in this trial:** unclear<br><br>**Number included in treatment group 1:** unclear (74% men, mean age 65, SD 14)<br><br>**Number included in treatment group 2:** unclear (31% men, mean age 64, SD 10)<br><br>**Number included in control group:** unclear (53% men, mean age 73, SD 8) | | functioning measured using MMSE | |
| Sun 2000 | **Study design:** parallel design<br>**Number of arms:** 2<br><br>**Experimental arm:** add-on psychotherapy<br><br>**Control arm:** usual care | **Geographical location:** China<br><br>**Setting:** not reported<br>**Number of participants:** 60<br><br>**Stroke criteria:** all ischaemic and haemorrhagic strokes<br><br>**Method of stroke diagnosis:** diagnosis consistent with diagnostic criteria for stroke reported in *Chinese Journal of Neurology and Psychiatry* in 1988 and confirmation by brain CT or MRI<br><br>**Inclusion criteria:** not reported<br><br>**Exclusion criteria:** (1) severe cognitive impairment; (2) obvious consciousness disturbance<br><br>**Depression criteria:** none<br><br>**Total number included in this trial:** 60<br><br>**Number included in treatment group:** 30 (60% men, mean age 56.5, SD 13.4, 53.3% ischaemic)<br><br>**Number included in control group:** 30 (63% men, 55.9, SD 14.3, 56.7% ischaemic) | **Treatment:** add-on psychotherapy entailing understanding the patient's reaction to sudden illness and letting the patient talk about concerns in mind, to give sympathy, care, and support; inducing correct understanding of the illness by the patient, helping him/her to analyse current problems and building confidence to overcome the disease; promoting the family's help and cooperation; giving praise, encouragement, or small prizes for patient improvement<br><br>**Administered by:** not reported<br><br>**Supervision:** not reported<br><br>**Intervention fidelity:** not reported<br><br>**Control:** usual care | • Depression - unclear what measure was used | Unable to isolate outcome data for those with depression at randomisation |
| Valiengo 2017 | **Study design:** parallel design<br><br>**Number of arms:** 2<br><br>**Experimental arm:** tDCS<br><br>**Control arm:** | **Geographical location:** Brazil<br><br>**Setting:** outpatient<br><br>**Number of participants:** 48<br><br>**Stroke criteria:** ischaemic and PICH stroke<br><br>**Method of stroke diagnosis:** diagnosis was confirmed with brain CT or MRI<br><br>**Inclusion criteria:** (1) aged 30 to 60 years; (2) first stroke only; (3) time since stroke < 5 years | **Treatment:** active tDCS. 12 times of 30-minute sessions of 2 mA anodal left/cathodal right dorsolateral prefrontal tDCS administered (once daily on weekdays for 2 weeks, then 1 session every other week)<br><br>**Control:** sham tDCS<br><br>**Duration:** 6 weeks<br><br>**Follow-up:** 2 weeks | • Depression measured using 17-item HDRS<br>• Clinical response (categorical, | Results not available in format suitable for this review |


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**Table 1. Characteristics of 'dropout' studies** *(Continued)*

| | | | |
|---|---|---|---|
| | sham tDCS | **Exclusion criteria:** (1) on antidepressants, antipsychotics, benzodiazepines, or diazepam; (2) dementia and epilepsy, life-threatening condition, suicide risk (score ≤ 2 on third item HDRS)<br><br>**Depression criteria:** depression diagnosed by a trained psychiatrist with the MINI for DSM-IV psychiatric disorders<br><br>**Total number included in this trial:** 48<br><br>**Number included in treatment group:** 24 (50% men, mean age 62.2, SD not reported)<br><br>**Number included in control group:** 24 (50% men, mean age 61.3, SD not reported) | defined as ≥ 50% reduction from baseline HDRS score)<br>• Remission (categorical, defined as an endpoint HDRS score < 8) |

BDI: Beck Depression Inventory.
BI: Barthel Index.
CES-D: Centre for Epidemiologic Studies Depression Scale.
CT: computed tomography.
DLPFC: dorsolateral pre-frontal cortex.
DSM- IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
ECT: electroconvulsive therapy.
EQ5D: EuroQoL 5-dimension.
FIM: Functional Independence Measure.
GDS: Geriatric Depression Scale.
HADS: Hospital Anxiety and Depression Scale.
HARS: Hamilton Anxiety Rating Scale.
HDRS: Hamilton Depression Rating Scale.
Hz: hertz.
LD: levodopa.
MADRS: Montgomery Asberg Depression Rating Scale.
MAO: monoamine oxidase.
MINI: Mini-International Neuropsychiatry Interview.
MMSE: Mini Mental State Examination.
MPH: methylphenidate.
MRI: magnetic resonance imaging.
mRS: modified Rankin Scale.
NIHSS: National Institute of Health Stroke Scale.
PICH: primary intracerebral haemorrhage.
PHQ-9: 9-item Patient Health Questionnaire.
rTMS: repetitive transcranial magnetic stimulation.
SAH: subarachnoid haemorrhage.
SD: standard deviation.
SF-36: Short-Form 36.
SNRI: selective nortriptyline reuptake inhibitor.
SSRI: selective serotonin reuptake inhibitor.
TIA: transient ischaemic attack.
tDCS: transcranial direct current stimulation.
ZDS: Zung Depression Scale.


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# APPENDICES

## Appendix 1. Search review - 2008

### Electronic searches

Cochrane Stroke Trial Register - searched October 2007; Cochrane Anxiety and Neurosis Trial Register - searched February 2008.

The remaining databases were searched May 2006.

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- Embase
- CINAHL
- PsycINFO
- Applied Science and Technology Plus
- Arts and Humanities Index
- Biological Abstracts
- BIOSIS Previews
- General Science Plus
- Science Citation Index
- Social Sciences Citation Index
- ISI Web of Science
- Dissertations and Theses

The following search strategy with a combination of controlled vocabulary and free-text terms for MEDLINE and CINAHL (Ovid), and modified 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/


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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

#### Additional searches

The following conference abstracts and proceedings were searched.

- European Stroke Conferences (2000 to 2007)
- Stroke Society of Australasia Annual Scientific Meetings (1999 to 2007)

Online clinical trials and research registries were also searched August 2007.

- www.strokecenter.org/trials
- www.ClinicalTrials.gov
- www.Clinicalstudyresults.org
- www.anzctr.org.au

#### Reference lists

Reference lists of relevant studies were searched to identify studies not already included.

#### Personal communication

Professional bodies, authors of included studies, and pharmaceutical companies were contacted for information on published and unpublished information.

## Appendix 2. Search review 2018 - CENTRAL

#### Search strategy for CENTRAL, August 2018

| # | Query |
|---|---|
| #1 | [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"] |
| #2 | stroke or poststroke or "post-stroke" or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplex* or SAH:ti,ab,kw (Word variations have been searched) |
| #3 | (brain* or cerebr* or cerebell* or intracran* or intracerebral) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*):ti,ab,kw (Word variations have been searched) |


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*(Continued)*

| | |
|---|---|
| #4 | (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*):ti,ab,kw (Word variations have been searched) |
| #5 | [mh hemiplegia] or [mh paresis] |
| #6 | hemipleg* or hemipar* or paresis or paretic:ti,ab,kw (Word variations have been searched) |
| #7 | #1 or #2 or #3 or #4 or #5 or #6 |
| #8 | [mh ^"depressive disorder"] or [mh ^"depressive disorder, major"] or [mh ^"depressive disorder, treatment-resistant"] or [mh ^"dysthymic disorder"] or [mh ^depression] or [mh "antidepressive agents"] |
| #9 | depress* or dysthymi*or dysphor*or antidepress*or anti-depress*:ti,ab,kw (Word variations have been searched) |
| #10 | #8 or #9 |
| #11 | #7 and #10 |

## Appendix 3. Search review 2018 - MEDLINE

### Search strategy for MEDLINE, August 2018

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. depressive disorder/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or Depression/ or exp Antidepressive Agents/
9. (depress$ or dysthymi$ or dysphor$ or antidepress$ or anti-depress$).tw.
10. 8 or 9
11. Randomized Controlled Trials as Topic/
12. random allocation/
13. Controlled Clinical Trials as Topic/
14. control groups/
15. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
16. double-blind method/
17. single-blind method/
18. Placebos/
19. placebo effect/
20. cross-over studies/
21. Therapies, Investigational/
22. Drug Evaluation/
23. Research Design/
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
27. (random$ or RCT or RCTs).tw.
28. (controlled adj5 (trial$ or stud$)).tw.


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29. (clinical$ adj5 trial$).tw.
30. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
31. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
32. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
33. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
34. (cross-over or cross over or crossover).tw.
35. (placebo$ or sham).tw.
36. trial.ti.
37. (assign$ or allocat$).tw.
38. or/11-37
39. 7 and 10 and 38
40. exp animals/ not humans.sh.
41. 39 not 40

## Appendix 4. Search review 2018 - Embase

### Search strategy for Embase, August 2018

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/
2. stroke patient/ or stroke unit/
3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
6. hemiparesis/ or hemiplegia/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. depression/ or agitated depression/ or atypical depression/ or dysphoria/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/
10. exp antidepressant agent/
11. (depress$ or dysthymi$ or dysphor$ or antidepress$ or anti-depress$).tw.
12. 9 or 10 or 11
13. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
14. Randomization/
15. Controlled clinical trial/ or "controlled clinical trial (topic)"/
16. control group/ or controlled study/
17. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
18. Crossover Procedure/
19. Double Blind Procedure/
20. Single Blind Procedure/ or triple blind procedure/
21. placebo/ or placebo effect/
22. (random$ or RCT or RCTs).tw.
23. (controlled adj5 (trial$ or stud$)).tw.
24. (clinical$ adj5 trial$).tw.
25. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
26. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
27. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
28. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
29. (cross-over or cross over or crossover).tw.
30. (placebo$ or sham).tw.
31. trial.ti.
32. (assign$ or allocat$).tw.
33. or/13-32
34. 8 and 12 and 33
35. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
36. 34 not 35


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## Appendix 5. Search review 2018 - PsycINFO

**Search strategy for PsycINFO, August 2018**

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebral small vessel disease/ or cerebrovascular accidents/ or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiparesis/ or hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. major depression/ or dysthymic disorder/ or endogenous depression/ or reactive depression/ or recurrent depression/ or treatment resistant depression/ or atypical depression/ or "depression (emotion)"/
9. exp antidepressant drugs/
10. (depress$ or dysthymi$ or dysphor$ or antidepress$ or anti-depress$).tw.
11. 8 or 9 or 10
12. clinical trials/ or treatment effectiveness evaluation/ or placebo/
13. treatment outcome clinical trial.md.
14. (random$ or RCT or RCTs).tw.
15. (controlled adj5 (trial$ or stud$)).tw.
16. (clinical$ adj5 trial$).tw.
17. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
18. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
19. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
20. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
21. (cross-over or cross over or crossover).tw.
22. (placebo$ or sham).tw.
23. trial.ti.
24. (assign$ or allocat$).tw.
25. or/12-24
26. 7 and 11 and 25

## Appendix 6. Search review 2018 - CINAHL

**Search strategy for CINAHL, August 2018**

| # | Query |
|---|---|
| S1 | (MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections") |
| S2 | (MH "Stroke Patients") OR (MH "Stroke Units") |
| S3 | TI ( stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH ) or AB ( stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH ) |
| S4 | TI ( brain* or cerebr* or cerebell* or intracran* or intracerebral ) or AB ( brain* or cerebr* or cerebell* or intracran* or intracerebral ) |
| S5 | TI ( ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* ) or AB ( ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* ) |
| S6 | S4 and S5 |


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(Continued)

| | |
|---|---|
| S7 | TI ( brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid ) or AB ( brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid ) |
| S8 | TI ( haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed* ) or AB ( haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed* ) |
| S9 | S7 and S8 |
| S10 | (MH "Hemiplegia") |
| S11 | TI ( hemipleg* or hemipar* or paresis or paretic ) or AB ( hemipleg* or hemipar* or paresis or paretic ) |
| S12 | S1 or S2 or S3 or S6 or S9 or S10 or S11 |
| S13 | (MH "Depression") OR (MH "Depression, Reactive") OR (MH "Dysthymic Disorder") |
| S14 | (MH "Antidepressive Agents+") |
| S15 | TI ( depress* or dysthymi*or dysphor*or antidepress*or anti-depress* ) OR AB ( depress* or dysthymi*or dysphor*or antidepress*or anti-depress* ) |
| S16 | S13 OR S14 OR S15 |
| S17 | (MH "Randomized Controlled Trials") or (MH "Random Assignment") or (MH "Random Sample+") |
| S18 | (MH "Clinical Trials") or (MH "Intervention Trials") or (MH "Therapeutic Trials") |
| S19 | (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies") |
| S20 | (MH "Control (Research)") or (MH "Control Group") or (MH "Placebos") or (MH "Placebo Effect") |
| S21 | (MH "Crossover Design") OR (MH "Quasi-Experimental Studies") |
| S22 | PT (clinical trial or randomized controlled trial) |
| S23 | TI (random* or RCT or RCTs) or AB (random* or RCT or RCTs) |
| S24 | TI (controlled N5 (trial* or stud*)) or AB (controlled N5 (trial* or stud*)) |
| S25 | TI (clinical* N5 trial*) or AB (clinical* N5 trial*) |
| S26 | TI ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*)) or AB ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*)) |
| S27 | TI ((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*)) or AB ((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*)) |
| S28 | TI ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*)) or AB ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*)) |
| S29 | TI (cross-over or cross over or crossover) or AB (cross-over or cross over or crossover) |
| S30 | TI (placebo* or sham) or AB (placebo* or sham) |
| S31 | TI trial |


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(Continued)

| | |
|---|---|
| S32 | TI (assign* or allocat*) or AB (assign* or allocat*) |
| S33 | TI controls or AB controls |
| S34 | TI (quasi-random* or quasi random* or pseudo-random* or pseudo random*) or AB (quasi-random* or quasi random* or pseudo-random* or pseudo random*) |
| S35 | S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 S36 .S12 AND S16 AND S35 |
| S36 | S6 AND S16 AND S35 |

## Appendix 7. Search review 2018 - Web of Science

### Search strategy for Web of Science, August 2018

The following indexes Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), and Arts & Humanities Citation Index (A&HCI) within Web of Science were searched from January 2002 to August 2018.

| # | Query |
|---|---|
| #1 | TS=(stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc* or cva* or apoplex* or SAH) |
| #2 | TS=((brain* or cerebr* or cerebell* or intracran* or intracerebral) NEAR/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*)) |
| #3 | TS=((brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) NEAR/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)) |
| #4 | TS=(hemipleg* or hemipar* or paresis or paretic or hemineglect or hemi-neglect) |
| #5 | TS=((unilateral or spatial or hemi*spatial or visual) NEAR/5 neglect) |
| #6 | #5 OR #4 OR #3 OR #2 OR #1 |
| #7 | TS=(depress* or dysthymi*or dysphor*or antidepress*or anti-depress*) |
| #8 | TS=(random* or RCT or RCTs) |
| #9 | TS=(controlled NEAR/5 (trial* or stud*)) |
| #10 | TS=(clinical* NEAR/5 trial*) |
| #11 | TS=((control or treatment or experiment* or intervention) NEAR/5 (group* or subject* or patient*)) |
| #12 | TS=(quasi-random* or quasi random* or pseudo-random* or pseudo random*) |
| #13 | TS=((control or experiment* or conservative) NEAR/5 (treatment or therapy or procedure or manage*)) |
| #14 | TS=((singl* or doubl* or tripl* or trebl*) NEAR/5 (blind* or mask*)) |
| #15 | TS=(cross-over or cross over or crossover) |


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*(Continued)*

| | |
|---|---|
| #16 | TS=(placebo* or sham) |
| #17 | TI=trial |
| #18 | TS=(assign* or allocat*) |
| #19 | TS=controls |
| #20 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 or #19 |
| #21 | #6 AND #7 AND #20 |

## Appendix 8. Search review 2018 - other sources

### Additional searches

The following conference abstracts and proceedings were searched.

1. European Stroke Conference (2011- 2018)
2. Stroke Society of Australasia Annual Scientific Meetings (2011- 2017)
3. World Stroke Congress (2000-2016)
4. Asia Pacific Stroke Conference (2011-2017)

Online clinical trials and research registers were also searched August 2018.

- www.ClinicalTrials.gov (https://clinicaltrials.gov/)

(depression OR low mood) AND (Brain Infarction OR Intracranial Hemorrhages OR Carotid Artery Diseases OR Brain Ischemia OR Cerebral Hemorrhage OR Cerebrovascular Disorders OR Stroke)

- WHO International Clinical Trials Registry Platform (https://www.who.int/ictrp/search/en/)

Condition: stroke AND depression OR low mood
Recruitment status is: ALL
Phases are: ALL

Hide synonyms
- 9-52 DEPRESSIVE DISORDERS, BEREAVEMENT, DEPRESSED, DEPRESSED - SYMPTOM, DEPRESSED MOOD, DEPRESSED MOOD (FINDING), DEPRESSED MOOD (PHYSICAL FINDING), DEPRESSED STATE, DEPRESSIVE DIS, DEPRESSIVE DISORDER, DEPRESSIVE DISORDER (DISORDER), DEPRESSIVE DISORDER [DISEASE/FINDING], DEPRESSIVE DISORDER NOS, DEPRESSIVE DISORDER, NOS, DEPRESSIVE DISORDERS, DEPRESSIVE DISORDERS NOS, DEPRESSIVE ILLNESS, DEPRESSIVE NEUROSES, DEPRESSIVE NEUROSIS, DEPRESSIVE STATE, DEPRESSIVE STATE NOS, DEPRESSIVE; DISORDER, DEPRESSIVE; NEUROSIS, DEPRESSIVE; STATE, DISORDER, DEPRESSIVE, DISORDER; DEPRESSIVE, DISORDERS, DEPRESSIVE, DYSTHYMIC DISORDER, FEELING BLUE, FEELING DOWN, FEELING;DOWN, LOW MOOD, MELANCHOLY, MISERABLE, MOOD DEPRESSED, MOOD DISORDER OF DEPRESSED TYPE, MOOD DISORDER OF DEPRESSED TYPE (DISORDER), MOROSE MOOD, NEUROSES, DEPRESSIVE, NEUROSIS, DEPRESSIVE, NEUROSIS; DEPRESSIVE, PUSH DOWN OR DEPRESS, STATE; DEPRESSIVE, depression - DEPRESSED, DEPRESSED MOOD, DEPRESSED MOOD (FINDING), DEPRESSED MOOD (PHYSICAL FINDING), FEELING BLUE, FEELING DOWN, FEELING;DOWN, MELANCHOLY, MOOD DEPRESSED, MOOD DEPRESSION, MOOD DEPRESSIONS, MOROSE MOOD, low mood - ACCIDENT CEREBROVASCULAR, ACCIDENT; CEREBRAL, ACCIDENT; CEREBROVASCULAR, APOPLEXY, APOPLEXY, CEREBROVASCULAR, APOPLEXY; CEREBRAL, BRAIN ATTACK, BRAIN VASCULAR ACCIDENT, BRAIN VASCULAR ACCIDENTS, CEREBRAL VASCULAR ACCIDENT, CEREBRAL VASCULAR EVENTS, CEREBRAL; ACCIDENT, CEREBRAL; APOPLEXY, CEREBROVASCULAR ACCIDENT, CEREBROVASCULAR ACCIDENT (DISORDER), CEREBROVASCULAR ACCIDENT NOS, CEREBROVASCULAR ACCIDENT, NOS, CEREBROVASCULAR ACCIDENTS, CEREBROVASCULAR APOPLEXY, CEREBROVASCULAR; ACCIDENT, CVA, CVA (CEREBRAL VASCULAR ACCIDENT), CVA (CEREBROVASCULAR ACCIDENT), CVA NOS, CVAS (CEREBROVASCULAR ACCIDENT), NEURO: CEREBROVASCULAR ACCIDENT, VASCULAR ACCIDENT, BRAIN, VASCULAR ACCIDENTS, BRAIN, stroke

## WHAT'S NEW


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| Date | Event | Description |
|---|---|---|
| 13 August 2018 | New search has been performed | New interventions are included: combination psychological and pharmacological interventions vs a single intervention, and non-invasive brain stimulation interventions<br><br>Thirty-three new trials (39 comparisons) with 2753 participants are included in the review. A total of 49 trials (56 comparisons) with 3342 participants are included in the review. Data were available for 20 pharmacological comparisons, 8 non-invasive brain stimulation comparisons, 16 psychological therapy comparisons, and 12 combination therapy trials<br><br>Covidence was used to collate and screen identified titles and abstracts<br><br>MH extracted additional data from previously included trials<br><br>Searches for the review were completed to 13 August 2018 |
| 13 August 2018 | New citation required and conclusions have changed | New data are included. New authors are included |

## HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 3, 2004

| Date | Event | Description |
|---|---|---|
| 28 March 2008 | Amended | Review was converted to new review format |
| 14 March 2008 | New search has been performed | Searches for the review were completed to February 2008<br><br>Seven new trials have been added: 6 pharmacological interventions, making a total of 13, and 2 psychological interventions, making a total of 4 comparisons. A total of 16 trials with 1655 participants are now included<br><br>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<br><br>There has been a change in authorship |

## CONTRIBUTIONS OF AUTHORS

SA: contributed to writing the review, completed title screening and inclusion/exclusion review, extracted data, performed meta-analyses and GRADE assessment.
KC: completed title screening and inclusion/exclusion review and data extraction.
CFH: assisted with obtaining, translating, and extracting data from Chinese studies for the current updated review.


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HL: completed title screening and cross-checked data extraction.
AH: conceived the idea for the review; contributed to development, writing, and editing of the protocol; and undertook the work necessary to complete the 2004 and 2008 reviews.
MH: contributed to development, writing, and editing of the protocol; undertook the work necessary to complete the 2004 and 2008 reviews; and oversaw each version of the review updates.

All review authors read and edited this update.

## DECLARATIONS OF INTEREST

SA: none known.
KC: none known.
C-FH: none known.
HL: none known.
AH: none known.
MH: 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.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, the review was expanded to include other non-invasive brain stimulation interventions such as (1) transcranial magnetic stimulation or repetitive transcranial magnetic stimulation (TMS or rTMS, where a magnetic 'coil' is placed near the head of the person receiving treatment without making physical contact); (2) transcranial direct current stimulation (tDCS, where a constant, low current is delivered directly to the brain area of interest via small electrodes); (3) cranial electrotherapy stimulation (CES, where a small, pulsed electrical current is applied across a patient's head); and (4) magnetic seizure therapy (MST), a type of convulsive therapy that involves replacing the electrical stimulation used in ECT with a rapidly alternating strong magnetic stimulation; and (5) combinations of all included interventions compared with a single intervention plus a respective control.

## 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


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