CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Rehabilitation, Recovery and Community Participation Following Stroke

Part Three: *Optimizing Activity and Community Participation following Stroke*

Evidence Tables

Management of Mood Disorders

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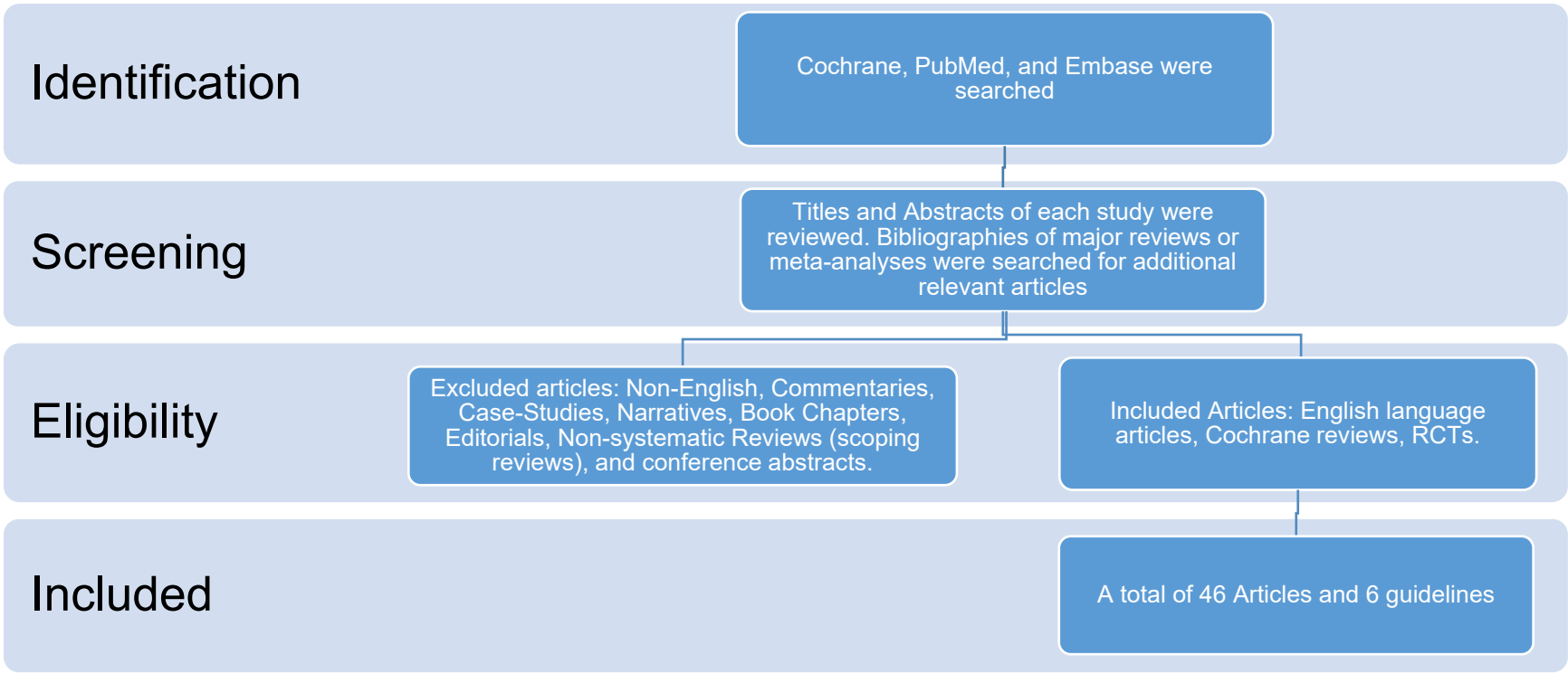
Search Strategy



Cochrane, PubMed and Scopus databases were searched using the terms ([stroke OR cerebrovascular disorders] AND [depression OR depressive disorders OR anxiety OR anxiety disorders OR emotional incontinence OR mood [AND antidepressant OR therapy OR psychotherapy]). The title and abstract of each article was reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 46 articles and 6 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Management of Stroke Rehabilitation Working Group. VA/DoD clinical practice guideline for the management of stroke rehabilitation. Washington (DC): Veterans Health Administration, Department of Defense; Version 5.0 – 2024. **Available at:** https://www.healthquality.va.gov/guidelines/Rehab/stroke/	38. There is insufficient evidence to recommend for or against solution-focused psychological interventions (e.g., motivational interviewing, problem-solving therapy) to prevent the development of depression. Neither for, nor against 39. We suggest against the use of antidepressants for the prevention of post-stroke depression. Weak (against) 40. We suggest offering a selective serotonin reuptake inhibitor or a serotonin norepinephrine reuptake inhibitor for treatment of post-stroke depression. Weak (for) 41. We suggest psychotherapy (e.g. cognitive behavioral therapy) for depression following stroke. Weak (for) 42. We suggest mindfulness-based therapies for treatment of depression following stroke. Weak (for) 43. There is insufficient evidence to recommend for or against acupuncture, either alone or as an adjunct to pharmacotherapy, for depression following stroke. Neither for, nor against
National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. **Available at:** www.strokeguideline.org. **(selected)**	B: People with stroke should be routinely screened for anxiety and depression using standardised tools, the results of which should be used alongside other sources of information to inform clinical formulation of treatment and support needs. F: People with depression or anxiety after stroke, and those assessed to be at risk, should be considered by the multidisciplinary team for non-pharmacological approaches, education and a reasonable period of watchful waiting where appropriate. H: People with stroke at significant risk of anxiety or depression should be offered psychological therapies (motivational interviewing, cognitive behavioural therapy, problem-solving therapy or acceptance and commitment therapy) provided they have sufficient cognitive and language skills to engage with the therapy. I: People with stroke should not be routinely offered SSRIs for the prevention of depression, but SSRIs may be considered when other preventative approaches are not appropriate (e.g. in people with severe cognitive or language impairment) or when the risk of depression is high (e.g. in people with a previous history of depression). The balance of risk and benefit from SSRIs should take account of the potential for increased adverse effects (seizures and hip fracture). J: People with depression after stroke should be offered psychological interventions (motivational interviewing, cognitive behavioural therapy or problem-solving therapy) adapted as necessary for use with people with aphasia or cognitive impairment and/or an SSRI. M: People with anxiety after stroke may be considered for medication therapy, after discussion between clinician and the person about adverse events and alternative treatment approaches including psychological interventions N: People with depression or anxiety after stroke who are treated with antidepressant medication should be monitored for effectiveness and adverse effects within the first 6 weeks. If there has been a benefit people should be treated for at least four months beyond initial recovery. If the person's mood has not improved after 6 weeks, medication adherence should be checked before considering a dose increase, a change to another antidepressant or an alternative non-pharmacological treatment

Guideline	Recommendations
Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. (Part 6)	Practice points Stroke survivors with suspected altered mood (e.g. depression, anxiety, emotional lability) should be assessed by trained personnel using a standardised and validated scale. Diagnosis should only be made following clinical interview Strong recommendation Updated For stroke survivors with depression or depressive symptoms, antidepressants, which includes SSRIs should be considered. There is no clear evidence that particular antidepressants produce greater effects than others and will vary according to the benefit and risk profile of the individual. Consensus-based recommendations For people with anxiety after stroke, psychological therapy and/or relaxation strategies, such as yoga may be trialed to reduce levels of anxiety. The addition of pharmacotherapy should be very carefully considered taking into account higher risk of harms
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110**	**4.9. Depression Screening** Administration of a structured depression inventory is recommended to routinely screen for poststroke depression, but the optimal timing of screening is uncertain. Class I; LOE B-NR. 4.9.2. Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness. Class I; LOE B-R
Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela BM et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and	**Summary of Findings** Twelve trials (n=1121 participants) suggest that antidepressant medications may be effective in treating PSD; further research is needed to determine optimal timing, threshold, and medications for treatment**.**

Guideline	Recommendations
Stroke Nursing; and Council on Quality of Care and Outcomes Research. **Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;48(2):e30-e43**	
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. **Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;47:e98–e169.** **(selected)**	Administration of a structured depression inventory such as the Patient Health Questionnaire-2 is recommended to routinely screen for poststroke depression. Class I; LOE B Periodic reassessment of depression, anxiety, and other psychiatric symptoms may be useful in the care of stroke survivors. Class IIa; LOE B Consultation by a qualified psychiatrist or psychologist for stroke survivors with mood disorders causing persistent distress or worsening disability can be useful. IIa; LOE C Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness. Class I; LOE B. A therapeutic trial of an SSRI or dextromethorphan/quinidine is reasonable for patients with emotional lability or pseudobulbar affect causing emotional distress. Class IIa; LOE A Combining pharmacological and nonpharmacological treatments of poststroke depression may be considered. Class IIb; LOE A. No recommendation for the use of any particular class of antidepressants is made. SSRIs are commonly used and generally well tolerated in this patient population. Class III;LOE A.

Evidence Tables

Incidence, Prevalence and Predictors of Post-Stroke Depression (PSD)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Shi et al. 2017 **China** **Systematic review & meta-analysis**	NA	36 studies including 14,791 persons with stroke who were followed over time for the development of depression.	Potential risk factors were identified from each study, and the results were pooled. Potential risk factors included sex, age, social support, history of mental illness, neuroticism, family history of mental illness, stroke severity, level of handicap, and independence, education, comorbidity, stroke location, and biochemical markers	**Primary outcome:** Risk factors for PSD	The duration of follow-up ranged from 2 weeks to 15 years. In pooled analyses, the odds of PSD were significantly higher in women (OR= 1.77, 95% CI 1.26–2.49, including 8 studies), age <70 years (OR=1.94, 95% CI 1.36–2.79, including 2 studies), in persons with a history of mental illness (OR=2.93, 95% CI = 1.42–6.05, including 6 studies), neuroticism (OR=1.08, 95% CI 1.03–1.14, including 3), a family history of mental illness (OR=1.95, 95% CI 1.33–2.87, including 2 studies), greater stroke severity (OR=1.12, 95% CI 1.08–1.16, including 6 studies), and a higher level of handicap (OR=1.52, 95% CI 1.32–1.75, including 4 studies). For all risk factors, assessments were conducted within the first 3 months post stroke. Increased social support was protective for the development of PSD (OR=0.93, 95% CI 0.87–0.99, including 3 studies).
Salinas et al. 2017 **USA** **Prospective study**	NA	1,424/161,808 postmenopausal women included in the Women's Health Initiative, aged 50-70 years, without a baseline history of stroke or depression (based on no antidepressant use or self-reported depression at enrollment) and who subsequently were diagnosed with an ischemic stroke, excluding TIA and minor stroke not requiring hospitalization.	The development of new onset post-stroke depression (NPSD) was established based on Burnam screening score ≥5, administered a minimum of 3 times during the study or the initiation of treatment for depression, within 5 years after incident stroke. The relationship between NPSD and pre-stroke psychosocial factors was examined.	**Primary outcome:** NPSD over 5 years post stroke **Secondary outcomes:** Subgroup analysis based on stroke subtype, stroke severity, and predictors of the NPSD	NPSD occurred in 21.4% (305) of participants. The median time from stroke to NPSD was 16.0 months (range=33 days–5 years). NPSD varied by stroke severity ranging from 16.7% of those with good recovery to 31.6% of those with severe disability. Participants with total anterior circulation infarction had the highest proportion of NPSD compared with those with lacunar infarcts, who had the lowest (31.4% vs. 16.1%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Among women with good recovery (i.e those able to return to work or school), the odds of NPSD within 5 years were significantly lower among those who were moderately optimistic those who had experienced fewer adverse life events.
Guiraud et al. 2016 **France** **Prospective Study** ***Depression Predictors after Ischemic Stroke (DEPRESS)***	NA	251 patients, aged ≥18 years, consecutively admitted to a stroke unit with a recent (<14 days) ischemic stroke. Patients with current depression or with moderate or severe cognitive impairment, were excluded.	Patients were screened for depression at baseline and at 2 and six-month visits, using The Patient Health Questionnaire (PHQ-9). The diagnosis was confirmed by a psychiatrist using the Mini International Neuropsychiatric Interview. In severely aphasic patients, depression was diagnosed using the Aphasic Depression Rating Scale (ADRS) and the Visual Analog Mood Scale (VAMS).	**Primary outcomes:** Incidence and predictors of depression at 6 months post stroke	The incidence of depression was 3% (n=7) at baseline, 19% (n=50) at 2 months and 24.3% (n=61) at 6 months. Independent predictors of depression included female gender, prior history of depression, physical disability (mRS score >2 at discharge), pathologic crying, and prior history of stroke. The presence of ≥2 predictors identified 62% of depressed patients. 15 patients could not be assessed at six months
Jorgensen et al. 2016 **Denmark** **Retrospective study**	NA	157,243 admissions for first-ever stroke or TIA among persons aged ≥15 years between 2001 and 2011, representing all stroke admissions to hospitals in Denmark. At baseline, 21,826 patients had current depression A population-based sample of 160,236 persons, matched for age, sex and municipality was used for comparison. At baseline, 14,737 persons had current depression.	The incidence of new-onset depression over 2 years was compared between persons with first-ever stroke and the general population. Early depression was defined as occurring between 0-3 months, intermediate depression between 3 months and one year and late depression between 1 and 2 years after study entry.	**Primary outcomes:** Incident depression, risk factors for depression and association between depression and mortality	The risk of incident depression was significantly higher among persons recovering from stroke at all assessment points. Analyses were adjusted for age, sex, education, cohabitation status, somatic comorbidities and previous depression Early depression: 13.1% vs. 1.7%, adj HR=8.53, 95% CI 8.17-8.91 Intermediate depression: 11.4% vs. 3.0%, adj HR=3.84, 95% CI 3.70-3.98 Late depression: 6.4% vs. 3.4%, adj HR=1.82, 95% CI 1.75-1.89 All incident depression during 2 years: 25.4% vs. 7.8%, adj HR=4.09, 95% CI 4.00-4.18 Independent predictors of depression for both

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					stroke and reference groups included older age, female sex, living alone, basic education, diabetes, high levels of comorbidity and a history of depression. Greater stroke severity was an additional predictor for the stroke group. The risk of mortality within 2 years among persons with new onset depression was significantly higher in the reference group (adj HR=3.75, 95% CI 3.51-4.00 vs. 1.89, 95% CI 1.83-1.95, p<0.01).
Hackett & Pickles 2014 **Australia** **Systematic review**	NA	61 prospective studies (n= 25,488 participants) including adult (>18 years) stroke survivors, who had undergone an assessment of depression or depressive symptom burden, performed at a pre-specified time-point. 30 studies were hospital based, 19 studies were rehabilitation based, 12 studies were population based. In most studies, all stroke types were included. A portion of the studies excluded participants with a history of depression, aphasia and/or recurrent stroke	Update to 2005 review (n=51 studies)	**Primary outcome:** Incidence of depressive disorder, depressive symptoms, or 'psychological distress and major/minor post-stroke depression	The overall pooled frequency estimate of PSD was 31%, 95% CI 28% to 35%. Timing of assessment (months post stroke): 0-1 month: 28%, 95% CI 23% to 33%, n=4,466 2-5 months: 36%, 95% CI 29% to 43%, n=18,254 6-9 months: 31%, 95% CI 26% to 37%, n= 2,224 1 year: 33%, 95% CI 26% to 39%, n=4,001 2-4 years: 25%, 95% CI 16% to 33%, n=2,408 5 years: 23%, 95% CI 14% to 31%, n=1,845 Subgroup analyses History of depression: 31%, 95% CI 27 to 35% (48 studies, n=23,654 people) Aphasia: 34%, 95% CI 29 to 39% (25 studies, n=19,218 people) First-ever stroke: 33%, 95% CI 28 to 38 (25 studies, n=5,658 people)
Ayerbe et al. 2011, 2013 **UK** **Prospective study**	NA	3,689 patients registered in the South London Stroke Register 1995 to 2006, following first stroke.	Development of depression was assessed at 3 months, 1, 3, and 5 years, using Hospital Anxiety and Depression Scale (HADS-D). Scores of >7 indicated depression, scores of >10 indicated severe depression. Data collected at follow-up also included accommodation,	**Primary outcomes:** Frequency of depression, and predictors	The percentage of participants who were depressed: 1 month: 33%, 95% CI 33–36%, n=1,821 1 year: 28%, 95% CI 25-30%, n=1,752 3 years: 32%, 95% CI 30-35%, n=1,353 5 years: 31%, 95% CI 27-34%, n=742 The percentage of participants with severe depression: 1 month: 15%, 95% CI 13-17% 1 year: 13%, 95% CI 11-15%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			employment, cognitive level, family support, activities of daily living, and activity.		3 years: 15%, 95% CI 13-17% 5 years: 12%, 95% CI 9-15% 48% of patients were not depressed at any time point; 49% to 55% of patients, depressed at 1 assessment remained depressed at follow-up; and 15% to 20% of patients at each assessment were new cases. Independent predictors of depression at 1 month, and 1-year post stroke were: GCS score 13-15, dysphagia, incontinence, impaired cognition (MMSE <24), inability to work and Barthel Index score of 20. Pre-stroke treatment for depression was an independent predictor at 3 months. Independent predictors of depression at 3 years post stroke were: dysphagia, incontinence, impaired cognition and Barthel Index score of 20. Independent predictors of depression at 5 years post stroke were: pre-stroke treatment for depression, impaired cognition and Barthel Index score of 20. **Up to 15-year follow-up** (1995-2009; n=4,022) From years 6-10, the incidence of post-stroke depression ranged from 13.2%-19.5%. From years 11-13, the incidence of post-stroke depression ranged from 15.9%-20.9%. At year 14, 1/15 patients at risk had incident depression. At year 15, 1/7 patients at risk had incident depression. Over 15 years, the prevalence of depression ranged from 29%-39%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Most cases of depression developed during the first 3 months post stroke (32.8%, 95% CI 30.0–35.6%). There were no new cases after 10 years.

Feasibility of Early Screening to Identify Possible Cases of Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Swartz et al. 2017 **Canada** **Feasibility study**	NA	1,503 patients attending a stroke prevention clinic between 2012-2014. Diagnoses included persons with stroke (29%) and TIA (34%). Persons were also referred for other non-stroke/TIA events. Mean age was 64 years, 53% were female.	The integrated DOC screening tool includes items to screen for obstructive sleep apnea (DOC-apnea), depression (DOC-mood) and cognitive impairment (DOC-Cog). The depression items included the PHQ-2 (scored 0-6). The reference standard was a Structured Clinical Interview for depression within 3 days of screening (minor and major depression)	**Primary outcome:** Feasibility (defined as 85% of patients completing the entire screen in ≤5 minutes) **Secondary outcome:** Validity	Feasibility: all patients completed the DOC screen 89% of patients completed the screen in less than 5 minutes. Mean time for completion was 4.2 minutes (range 1.6-15.8 minutes) Validity: 421 patients completed a SCID. The prevalence of any depression was 20.4%. 248 patients (59%) scored 0 and were considered to be at low risk of depression; 132 patients (31%) scored 1-3 and were considered to be at intermediate risk of depression and 42 persons (10%) scored ≥4 and were considered to be at high risk of depression. Using 2 cut-points, a score of 4-6 (high-risk) was associated with a specificity of 99% and PPV of 90%; a score of 0 (low-risk) was associated with a sensitivity of 92% and a NPV of 97%. AUC was 0.898, which increased to 0.902 after controlling for age, sex and education.
Karamchandani et al. 2015 **USA** **Retrospective study**	NA	303 patients admitted to a single institution over a 2.5-month period with ischemic or hemorrhagic stroke. Mean age was 63.9 years, 45% were female. Median NIHSS score was 9.	Patients who were deemed to be potentially eligible for depression screening were identified. A modified version of the Patient Health Questionnaire (PHQ-9), was used to screen for potential depression (defined as	**Primary outcome:** Feasibility (defined as >75% of eligible patients screened)	211 (70%) patients were eligible for screening. Of these, 75% (158) were screened. Median time from admission to screening was 2.5 days. 92 patients were not eligible for screening due to aphasia (n=30) or medical condition (n=62)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			score >4) before hospital discharge or transfer to another service.		including death, hospice/comfort measures, or prolonged intubation. 48 potentially eligible patients were missed (screen not ordered, or ordered and not completed) and in 5 patients, screening was attempted, but could not be completed. 56 patients (35%) were identified as depressed PHQ-9 scores 33 patients (20.9%) scored 0 69 patients (43.7%) scored 1-4 49 patients (31.0%) scored 5-14 7 patients (4.4%) scored ≥14

Validity of Screening Tools to Identify Possible Cases of Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prisnie et al. 2016 **Canada** **Prospective study**	NA	122 adult patients with stroke or TIA, consecutively recruited from an outpatient stroke prevention clinic, without severe aphasia, dementia or moderate/severe developmental delay. Mean age was 60.1 years, 55.7% were female. Mean time from index event onset was 3.6 months.	Participants completed a demographic questionnaire and 4 depression screens (assigned in random order), including Patient Health Questionnaire (PHQ)-9, the PHQ-2, the Hospital Anxiety and Depression Scale (HADS-D), and Geriatric Depression Scale (GDS-15. Each participant then completed the Structured Clinical Interview for DSM-IV (SCID) by telephone, conducted within 2 weeks of questionnaire completion, which was used to assess the presence of: current and past major depressive episode (MDE), current and past manic episode, dysthymic disorder, and adjustment disorder.	**Primary outcomes:** Sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predicative value (NPV), +/- likelihood ratios (LR) and Area under curve (AUC), based on optimal cut-points for each screening tool	The prevalence of SCID-diagnosed current major depressive episodes was 9.8% (n=12). 4 patients had MDE, 7 patients with depression had a previous history of depression. No patients had a current manic episode or an adjustment disorder. **Diagnostic Accuracies** PHQ-9 (cut point 13): SN: 81.8%; SP: 97.1%; PPV: 75.0%; NPV: 98%; +LR: 28.1; overall accuracy: 95.6% PHQ-2 (cut point 3): SN: 75.0%; SP: 96.3%; PPV: 96.2%; NPV: 97.2%; +LR: 20.1; overall accuracy: 94.1% HADS-D (cut point 10): SN: 63.6%; SP: 98.1%; PPV: 77.8%; NPV: 96.3%; +LR: 33.4; overall accuracy: 94.8% GDS-15 (cut point 7): SN: 45.5%; SP: 84.8%; PPV: 25.0%; NPV: 93.3%; +LR: 3.0; overall accuracy: 80.9% AUC: PHQ-9 86.6%, PHQ-2 86.7%, HADS-D 85.9%, and GDS-15 66.3%.
Meader et al. 2014 **UK** **Systematic review**	Using the QUADAS-2 tool, the most common risks of bias were for not reporting blinding of assessments, not reporting predefined cut-offs for	24 studies (n=2,907 participants) in which persons were screened for post-stroke depression. Sample sizes ranged from 27 to 423. Mean ages ranged from 55 to 80 years. The median prevalence for any depression was 18% (range 8–46%).	The performance of 18 previously validated screening tools to detect depression and major depression, using the International Classification of Disease or Diagnostic and Statistical Manual diagnosis of depression, as the reference standard.	**Primary outcomes**: Sensitivity (SN), specificity (SP), positive predictive values (PPVs) and negative predictive values (NPVs) and clinical utility, calculated using the clinical utility index (CUI)	**For the Identification of any depression** Meta-analysis was possible for 9 scales Including: Beck Depression Inventory (BDI); Center of Epidemiological Studies-Depression Scale (CES-D); Geriatric Depression Scale (GDS); Hospital Anxiety and Depression Scale (HADS), total and depression subscores; Hamilton Depression Rating Scale (HDRS); Montgomery Asberg Depression Rating Scale (MADRS) and Patient Health Questionnaire (PHQ).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	diagnostic thresholds and a lack of information concerning drop out				The 3 best performing scales included: CES-D (SN 0.75; 95% CI 0.60 to 0.85; SP 0.88; 95% CI 0.71 to 0.95), HDRS (SN 0.84; 95% CI 0.75 to 0.90; SP 0.83; 95% CI 0.72 to 0.90) and the PHQ-9 (SN 0.86, 95% CI 0.70 to 0.94; SP 0.79, 95% CI 0.60 to 0.90). All scales were rated as fair to poor for their Rule-in CUI. 7/9 scales were rated as good for their Rule-out CUI. **For the Identification of major depression** Meta-analysis was possible for 6 scales. The 2 best performing scales included: HDRS (SN 0.86; 95% CI 0.72 to 0.93; SP 0.89; 95% CI 0.79 to 0.96) and the PHQ-9 (SN 0.86, 95% CI 0.70 to 0.94; SP 0.79, 95% CI 0.60 to 0.90). All scales were rated as fair to poor for their Rule-in CUI. 7/9 scales were rated as good for their Rule-out CUI.

Pharmacological, Psychological, and Non-invasive Brain Stimulation Interventions for Treating Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Allida et al. 2023 **Australia** **Cochrane review**	Using the Cochrane RoB tool, the percentage of trials at low or unclear risk of bias were: Selection bias (random allocation) 95%; selection bias (concealed allocation) 80%; performance bias (blinding of participants/personnel) 70%; detection bias (blinding of outcome assessor) 85%; and attrition bias (incomplete reporting of data) 60%; All trials were at high or unclear risk of reporting bias (selective reporting)	65 RCTs (72 comparisons) including 3,342 participants with post-stroke depression, including depressive disorder, major depression and dysthymia or minor depression. All trials in which participants were not depressed at baseline, were excluded. The mean age of participants ranged from 52 to 78 years. Time since stroke and randomization ranged from 'within a few days' to >one year post stroke.	The interventions/control groups included: Pharmacological intervention vs. placebo (n=18 trials/20 comparisons). Pharmacological interventions included SSRIs (n=12), tricyclic antidepressants (n=2), and other agents (deanxit, aniracetam, reboxetine, trazodone and nefiracetam, n=6) Non-invasive brain stimulation (NIBS) vs. sham stimulation or usual care (n=8 trials/9 comparisons). Psychological therapy (including cognitive behavioral therapy, motivational interviewing, vs. usual care and/or attention control (n=22 trials/32 comparisons). Pharmacological intervention + various forms of psychological therapy vs. pharmacological intervention + usual care and/or attention	**Primary outcomes:** Risk of depression (using trial criteria) at the end of treatment, < 50% reduction in depression scale scores at the end of treatment **Secondary outcomes:** Death, adverse events at the end of treatment	*Pharmacological intervention vs. placebo* The risk of depression at the end of treatment was reduced significantly with pharmacological therapy (RR=0.70, 95% CI 0.55 to 0.88, 8 trials, n=1,025; GRADE: very low). Pharmacological interventions were associated with a < 50% reduction in depression scale scores at end of treatment (RR= 0.48, 95% CI 0.32 to 0.70; 6 trials, n=511; GRADE: very low). The risk of death associated with pharmacological therapy was not increased significantly (RR=0.64, 95% CI 0.20 to 2.07, 9 trials, n=848; GRADE: very low). The risk of any adverse event was increased significantly with pharmacological therapy (RR=1.55, 95% CI 1.12 to 2.15, 5 trials, n=488; GRADE: very low). While doses and duration of treatment was not summarized, the authors noted that the interventions in most trials were probably not given for an adequate length of time to show maximal or sustained response. *NIBS vs. sham stimulation or usual care* The risk of depression at the end of treatment was not reduced significantly with NIBS (RR=0.67, 95% CI 0.39 to 1.14, 2 trials, n=130; GRADE: very low). NIBS treatment did not reduce depression scale scores by <50% (RR=0.84, 95% CI 0.52 to 1.37, 2 trials, n=130; GRADE: very low).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			control (n=3 trials/3 comparisons) NIBS + pharmacological intervention vs. pharmacological intervention + sham stimulation or usual care (n=14 comparisons). Summary data on details of the interventions were not provided (e.g., dose, duration)		The risk of adverse events was not increased significantly with NIBS (RR=0.61, 95% CI 0.23 to 1.64, 4 trials, n=183; GRADE: low) The duration of treatment in these trials was short, ranging from one to 4 weeks. In most trials repetitive transcranial magnetic stimulation (rTMS)was the most common form of NIBS used. *Psychological therapy vs. usual care/attention control* The risk of depression at the end of treatment was reduced significantly with psychological therapy (RR=0.77, 95% CI 0.62 to 0.95, 6 trials, n=521; GRADE: very low), but not at the end of follow-up (RR=0.85, 95% CI 0.59 to 1.21, 3 trials, n=201; GRADE: very low) No data were available from primary studies to enable pooling of results of the other co-primary outcome. The risks of death or adverse events at the end of treatment were not increased significantly with therapy (RR=0.65, 95% CI 0.26 to 1.66, 8 trials, n=831 and RR=0.83, 95% CI 0.42 to 1.63; 8 trials, n=784; GRADE: very low for both outcomes). *Pharmacological intervention + psychological therapy vs. usual care* No data were available from primary studies to enable pooling of results of primary or secondary outcomes. *NIBS + pharmacological intervention vs. pharmacological intervention + sham stimulation* Combined therapy significantly reduced the risk of depression at the end of treatment

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(RR=0.77, 95% CI 0.64 to 0.91, 3 trials, n=392; GRADE: low). Combined treatment was not associated with a significantly reduced risk of a <50% reduction in depression scale scores (RR= 0.95, 95% CI 0.69 to 1.30, 3 trials, n=392; GRADE: very low). The risks of death or adverse events at the end of treatment were not increased significantly with combined therapy (RR=1.06, 95% CI 0.27 to 4.16, 5 trials, n=487 and RR=0.50, 95% CI 0.05 to 5.28; 3 trials, n=342; GRADE: very low for both outcomes).

Pharmacotherapy for the Treatment of Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Meta-analyses					
Xu et al. 2016 **China** **Systematic review & meta-analysis**	The overall quality of studies was rated as moderate, although some reports did not provide details about randomization, allocation concealment, or blinding	11 RCTs (n=740) including patients with a clinical diagnosis of post-stroke depression (PSD). Sample sizes ranged from 17-229. Mean age was 67.1 years, 47.6% were female. Criteria to establish depression included DSM III or IV (n=5), Hamilton Depression Scale score>15 (n=1), DSM +depression scale score>cut off (n=2), ICD-10 (n=1), other (n=1) and not reported (n=1)	Trials compared treatment with an antidepressant(s) vs. placebo. Mean duration of treatment was 10 weeks. Agents included SSRIs (n=7), TCAs (n=3) and other (n=2). Two trials compared 2 agents with placebo.	**Primary outcome:** Mean change in depression scores from baseline **Secondary outcome:** Treatment response	Treatment with an antidepressant was associated with a significant reduction in depression scores (SMD=-0.96, 95% CI -1.41 to -0.51, p<0.0001). Response to treatment was significantly higher with active treatment (RR=1.36, 95% CI 1.01-1.83, p=0.04). In subgroup analyses, younger age (<70 years) and female sex were associated with better response to treatment (i.e. greater reductions in depression scale scores). Persons receiving active treatment were significantly more likely to withdraw from studies due to adverse events (RR=2.72, 95% CI 1.37-5.43, p=0.004).
Placebo-controlled Trials of Pharmacotherapy					
Robinson et al. 2008 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	159 patients (10 days – 3 months post stroke) with a DSM-IV diagnosis of "depression due to stroke with major depressive-like episode" and a HRSD score ≥18. Mean ages were 66.8, 64.7 and 68.1 in the placebo and 2 treatment groups, respectively. 53.5% were female. There were no significant between group differences noted at baseline.	Participants were randomly assigned to receive 1 of 3 treatments for 12 weeks: i) 600 mg nefiracetam (n=55), ii) 900 mg nefiracetam (n=48) or iii) matching placebo.	**Primary outcome:** Change in depression severity, assessed by the Hamilton Rating Scale for Depression (HRSD) at the end of treatment.	There was no significant time x treatment effect of 600 mg or 900 mg nefiracetam when compared with placebo. There were no significant effects identified on an item-by-item analysis of the HRSD. A *post hoc* analysis identified a significant effect of treatment among the most severely depressed quintile of patients treated with 900 mg nefiracetam compared with placebo (p=0.05). Among participants who had completed at least 4 weeks of treatment (n=137), response rates (i.e. >50% decline in HRSD scores) were 76.5%, 71.8% and 71.4% for the 800 mg, 600 mg and placebo groups, respectively.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Remission rates (HRSD scores of ≤8 at the end of treatment) were 41.2%, 43.6% and 40.5% for the 900, 600 mg and placebo groups, respectively. No assessment of adverse events was reported.
Choi-Kwon et al. 2006 **South Korea** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	152 stroke patients with one of post stroke depression (average of 14 months post stroke), emotional incontinence or anger proneness. Individuals with SAH, severe communication problems, scored ≤23 on MMSE, or who had a history of depression prior to stroke, were excluded. Mean age was 58 years, 77% were male.	Participants were randomly assigned to receive either treatment with fluoxetine 20 mg/day (n=76) or matching placebo (n=79) in a single morning dose for 3 months.	**Primary outcomes:** Mean score on Beck Depression Inventory (BDI) for PSD, and percentage change in VAS score for emotional incontinence and anger proneness, at 3 and 6 months.	There was complete data at 3 and 6 months follow-up for 64 patients in the placebo group and 61 patients in the fluoxetine group. A total of 32 patients in the treatment group and 19 patients in the control group were diagnosed with PSD. The severity of PSD was judged to be mild (mean BDI = 19). Over time, there was a trend identified toward a decrease in depressive symptoms in both the treatment and the control condition. Treatment with fluoxetine was not associated with a significant improvement in depression at follow-up. There were no significant between group differences reported in terms of adverse events reported. Effects reported in the fluoxetine group included nausea, headache, insomnia, GI discomfort, decreased appetite.
Murray et al. 2005 **Sweden** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	123 stroke patients identified from 4 Swedish stroke centres with either a major (n=76) or minor (n=47) depressive episode (defined according to the DSM-IV), an average of 128 days after stroke. Mean age was 71 years, 47% were male.	Participants were assigned to either the treatment or placebo conditions. 62 patients received sertraline (50 – 100 mg/day) and 61 received a matching placebo for 26 weeks.	**Primary outcome:** Change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to weeks 6 and 26. **Secondary outcomes:** Emotional Distress Scale (EDS), Change in perceived Quality of Life (QoL)	Both groups demonstrated significant improvements in depressive symptoms over time, but there were no significant differences between groups in change in MADRS scores over the treatment period. There was a significantly greater improvement in EDS score at 6 weeks, favouring treatment with sertraline ($p<0.05$), but not at 26 weeks. Improvement in perceived QoL was significantly greater for patients treated with

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					sertraline at week 26 compared with the control group (p<0.05), but not at 6 weeks.
Rampello et al. 2005 **Italy** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	31 outpatients recruited within 12 months of ischemic or haemorrhagic stroke who also had a diagnosis of major or minor depression according to DSM-IV criteria in addition to the presence of retarded depression. Mean age was 77 years, 45% were male. Mean time since stroke was approximately 12 weeks.	Patients were randomly assigned to receive either treatment with, 4 mg, bid of reboxetine (n=16) or a matching placebo (n=15) for 16 weeks. Side effects reported by patients were recorded at each visit and patients were asked whether they remembered to take their medication regularly.	**Primary outcome:** "efficacy", defined as 1) variations in Hamilton Depression Rating Scale (HRSD) and Beck Depression Inventory (BDI) scores and 2) variations in the Synoptic Table Scores (used to distinguish retarded from anxious depression), assessed at baseline, 4, 8 and 16 weeks.	Patients in the treatment condition experienced significant improvement from baseline to 4, 8 & 16 weeks on both the HDRS and BDI (p<0.01 for all comparisons), while there was no significant change reported for patients who were assigned to receive placebo. At each assessment point, between group comparisons revealed significant reduction in HRSD scores in the group of patients assigned to treatment with reboxetine when compared to placebo (p<0.01 at 4, 8 and 16 weeks). The numbers of the most commonly reported side effects were similar between groups: dryness of feces, constipation, hyperperspiration, hypotension and sinusal tachycardia.
Fruehwald et al. 2003 **Austria** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	54 patients admitted to 2 hospitals following acute stroke, diagnosed with moderate to severe post-stroke depression Individuals with significant communication impairments or more than mild cognitive impairments were not included in the study. Mean age was 64 years, 58% were male. Mean time from stroke onset was 11 days.	Patients were randomly assigned within 2 weeks of stroke to receive treatment with either 20-40 mg fluoxetine (n=26) or matching placebo (n=24) for 12 weeks. If at the 4-week evaluation, the participant did not demonstrate response (ie. HDS >13), treatment was continued at a doubled dose, for an additional 8 weeks.	**Primary outcome:** Average change in Hamilton Depression Scale (HDS) score 4 weeks after treatment **Secondary outcomes:** Average changes in HDS at 3 months and at long-term follow-up (18 months), the average changes in Beck Depression Inventory (BDI) and the number of responders (patients with an HDS < 13).	Both groups demonstrated significant within group improvement over 4 weeks, but the difference between groups was not significant. Mean HSD scores decreased from 32.8 to 14.7 in the fluoxetine group vs. 30.3 to 11.7 in the placebo group. At 18 months, the mean HDS and BDI scores were significantly lower in the fluoxetine group (10.8 vs. 22.2, p<0.05, and 5.3 vs. 8.5, p<0.05, respectively). The mean change in HDS scores was significantly greater in the fluoxetine group (-22.2 vs. -8.8, p<0.05). At 18 months, the percentage of responders was significantly higher in the fluoxetine group (81.8% vs. 27.8%, p<0.01).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					No major side effects were reported. Minor effects reported by participants included dizziness, nausea and cephalalgia.
Wiart et al. 2000 **France** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	31 patients with a recent (within 3 months) ischemic stroke who were hemiplegic, with a diagnosis of major depressive disorder. Patients with a history of multiple strokes, severe aphasia and/or cognitive impairment were excluded. Mean age was 67 years. Mean time since stroke onset was 47 days.	Participants were randomly assigned to receive treatment with either 20 mg fluoxetine (n=16) or matching placebo (n=15) for 45 days (6 weeks).	**Primary outcome:** Changes in standardized test scores at days 15, 30 and 45. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Other measures included the Motricity Index and FIM	At the end of 6 weeks, participants in the fluoxetine demonstrated greater improvement on MADRS scores (-16.6 vs. -8.4, p<0.02). Response rates were non-significantly higher in the fluoxetine group (62.5% vs. 33.3%, p=0.1). There were improvements in function demonstrated by both groups, but no significant differences between groups. Side effects reported by individuals assigned to fluoxetine included, nausea, seizure, tremor, confusion, increased transaminases.
Robinson et al. 2000 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	56 adults, aged 18-85 years recovering from stroke with onset of <6 months, diagnosed with major or minor depression (based on DSM IV criteria or Hamilton Depression Scale score <12. Mean ages ranged from 64-73 years across treatment groups. Mean time from stroke onset ranged from 5-6 weeks. 48 individuals with no diagnosis of depression were enrolled in the study in order to assess effects of antidepressant use on recovery.	Participants were randomized to receive either fluoxetine (10mg/d gradually increased to 40 mg/day, n=23) or nortriptyline (dose of 25 mg/day gradually increased to 100 mg/day, n=16) or placebo (n=17) for 12 weeks. Participants then crossed over to 12 weeks of placebo treatment.	**Primary outcome:** Hamilton Rating Scale for Depression (HRSD-28), assessed at baseline and at each 3-week evaluation point. **Secondary outcome:** Successful response to treatment, defined as a >50% reduction in the HRSD scale score + failure to fulfill the criteria for major or minor depression.	Patients treated with nortriptyline had greater declines in HRSD scores compared with those treated with either fluoxetine or with placebo at 12 weeks follow-up, after adjustment for baseline differences in HRSD scores. The rate of successful treatment was 77% in the nortriptyline group, 14% in the fluoxetine group and 31% in the placebo condition. Neither depressed nor non-depressed patients in either active treatment condition demonstrated significant greater improvement in functional recover than those assigned to placebo. Adverse events included weight loss (fluoxetine in elderly patients), anxiety, insomnia and GI symptoms
Andersen et al. 1994	CA: ☒	66 patients, aged 18-80 years, recovering from stroke with moderate	Patients were randomized 1:1, to receive the “recommended” dose of citalopram (20 mg for	**Primary outcome:** Hamilton Depression Scale (HDS) and the	Treatment with citalopram was associated with significantly greater improvement in HDS scores over 6 weeks (mean change of -8.0

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Denmark **RCT**	Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	depression (defined as a baseline Hamilton Depression Scale score ≥ 13 and symptom duration of at least 2 weeks), enrolled 2 to 52 weeks after stroke. Mean age was 67 years, 39% were male. Mean time from stroke onset was 12 weeks.	those <66 years, or 10 mg for those individuals ≥66 years) for 6 weeks. At that point, for non-responders (defined as HRSD scores > 13), participants were offered treatment with either nortriptyline or mianserin. For responders (HRSD scores < 13), treatment was continued for an additional 10 weeks.	Melancholia Scale, assessed 6 weeks after treatment **Secondary outcome:** Response rate, defined as a decrease of >50% on HDS scores	±6.0 vs. -4.8 ±4.6, p<0.05) and on the Melancholia Scale (-7.2±5.8 vs. 4.3±4.1, p<0.05). At 6 weeks, the percentage of responders was significantly greater in the citalopram group (59% vs. 28%, p<0.05). At 16 weeks, the mean HDS score was significantly lower in the citalopram group (6.2±2.3 vs. 8.7±2.2, p<0.05). There number of adverse events was similar between groups.
Reding et al. 1986 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☒	27 patients with or without depression, enrolled in an inpatient stroke rehabilitation program. Among the patients recruited, unknown numbers had a clinical diagnosis of depression at baseline. Depression was identified by an abnormal Zung Depression Scale score, or an abnormal dexamethasone suppression test (DST). Mean ages across these groups ranged 63-73 years, mean days from stroke onset ranged from 24 to 51 days.	Participants were randomly assigned to receive either trazodone (200 mg daily, maximum dose, n=14) or placebo (n=13) for the duration of their rehabilitation stay.	**Primary outcome:** Improvement in Barthel Index (BI) scores, at end of treatment	The mean duration of treatment was 32 days (trazadone) and 25 days (placebo) For patients with a clinical diagnosis of depression at baseline, there was a non-significantly greater improvement in mean BI scores for patients receiving trazadone (28±7 vs. 20±7, p=n/s). Among patients with an abnormal Zung score, the mean improvement in BI scores was non-significantly greater in the trazadone group (46±5 vs. 18±9, p=n/s). Among patients with an abnormal DST, the mean improvement in BI scores was significantly greater in the trazadone group (38±6 vs. 20±6, p<0.05). The study was discontinued for 6 patients in the placebo group AND 6 patients in the trazodone group, due to perceived side effects of. In the trazodone group, these effects included sedation, and eye discomfort.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lipsey et al. 1984 **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	34 stroke patients with mild or major depression.	Participants were randomized to receive 20 -100 mg nortriptyline (n=14) or placebo (n=20) for 6 weeks.	**Primary outcome:** Change in Hamilton Depression Scale (HDS) and Zung Depression Scale scores by end of treatment **Secondary outcome:** Response rate	Patients who were treated with nortriptyline showed significantly greater improvement on the HDS and Zung Scale. Among participants who completed the trial, the response rate was 100% for nortriptyline and 33% for placebo.

Psychotherapy for the Treatment of Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mitchell et al. 2009 **USA** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor ☑ ITT:☑	101 patients recruited within 4 months of an ischemic stroke event and who were verified as depressed following a diagnostic interview based on the DSM-IV criteria. Mean age was 57 years, 59% male. Approximately 70% reported one episode of pre-stroke depression. 60% were taking an antidepressant at the time of study entry.	Patients were randomized to receive either a brief psychosocial, problem-solving intervention + possible antidepressant medication (n=48) or usual care + possible antidepressant medication (n=53). The psychosocial intervention consisted of 9 sessions over 8 weeks of problem-solving therapy and increased pleasant social and physical activity provided by a study (nurse) interventionist. Patients allocated to usual care were treated by stroke care provider.	**Primary outcome:** Reduction in the severity of depression symptoms, assessed using the Hamilton Depression Scale (HDS) at 12 months post stroke, remission of depression at 12 months (HDS<10) **Secondary outcomes:** Stroke Impact Scale SIS) at 12 months	At one year, the mean decrease in symptoms of HDS scores was significantly greater in the treatment group than in the control group (-9.2±5.7 vs. -6.2±6.4, p=0.023). At 24 months, there was no longer a significant difference between groups. Assignment to the treatment condition was associated with significantly greater odds for remission of depression immediately following treatment (OR=4.8, 95% CI 1.8- 12.9, p=0.001), at 21 weeks (OR=3.4, 95% CI 1.3-8.7, p=0.008) and at 12 months (OR=2.7, 95% CI 1.1- 6.6, p=0.031), but not at 24 months. At 12 months, participants who achieved remission had significantly better total SIS scores compared to those who remained depressed (74.5 vs. 52.6, p<0.01). 77% of each group reported the use of an antidepressant during the 8-week intervention period. The most commonly prescribed drugs were sertraline, citalopram and paroxetine.
Watkins et al. 2007 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT:☑	411 inpatients with stroke. Mean age was 68 years, 58% were men. Median LOS was 15 days. At baseline, 37% of patients were not depressed (GHQ-28 <5).	Between days 5 and 28 poststroke, patients were randomized to receive motivational interviewing (MI: 4 weekly appointments lasting 30-60 minutes, delivered by nurses and non-clinical psychologist) or usual care.	**Primary outcome:** General Health Questionnaire-28 (GHQ-28) **Secondary outcomes:** Yale Depression Screen (yes/no), Barthel Index (BI) Assessments were conducted at baseline and 3 months	Of the patients allocated to intervention, 146 (71.6%) received 4 motivational interviewing sessions, and 16 (7.8%) received no sessions. At 3 months, the odds of normal mood (GHQ-28 <5) were significantly higher in the MI group (54.7% vs 41.9%; OR=1.60, 95% CI 1.04 to 2.46). The odds of not being depressed based on the Yale screen were significantly higher in the MI group (52.9% vs. 42.5%; OR=1.65, 95% CI 1.06 to 2.58).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					There were no differences in the proportions of patients classified as mild, moderately or severely disabled using BI classification between groups.
Lincoln & Flannaghan 2003 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT:☒	123 stroke patients identified via hospital records who were either living at home, in hospital or living in long-term care one-month post stroke with >10 score on Beck Depression Inventory (BDI) or >18 on Wakefield Depression Inventory (WDI). There were 60 patients with a primary diagnosis of major depression at baseline. Mean age of patients was 65 ±15.1 in the no intervention group, 66.1±13.2 in the attention group and 67.1±12.7 in the CBT group. 51% of participants were male. Potential participants were excluded if they scored ≤23 on the MMSE.	Participants were randomly allocated to one of 3 conditions: 1) no intervention (n=41), 2) attention placebo (n=43) and 3) CBT (n=39). Patients in condition 1 had no further contact with the community psychiatric nurse. Patients in the attention placebo (2) condition received 10, 1-hour visits over 3 months by the community psychiatric nurse in which they discussed daily life, consequences and changes associated with stroke. In the CBT (3) condition, participants received 10, 1-hour sessions over 3 months by the community psychiatric nurse who used techniques such as education, graded task assignment, activity scheduling and identification and modification of unhelpful thoughts/beliefs – tailored to individual participants.	**Primary outcomes:** BDI and WDI **Secondary outcomes:** EADL scale, LHS and a rating of satisfaction of care. Assessments were conducted at baseline, 3- and 6-months post-randomization.	Examination of between group differences at baseline revealed no significant differences except that there were significantly more individuals with a diagnosis of major depression (ICD-10) allocated to receive CBT than either attention control or no intervention ($p<0.05$), although there were no significant differences in the BDI or WDI scores between groups at the time of study entry ($p=0.2$ and $p=0.2$, respectively). Mean number of CBT sessions delivered to participants was 9.85 (±2.31). Mean number of attention control sessions delivered was 10 (±0.55), but there was no significant between group difference reported in number of sessions received. For the primary study outcomes, the authors reported no significant difference on either the BDI or WDI at 3 months ($p=0.5$, $p=0.9$, respectively) or at 6-month follow-up ($p=0.6$, 0.4, respectively). 32% of the patients recruited did receive antidepressant therapy at some point during the study period. No between group differences were found in terms of the proportion of participants receiving antidepressant therapy.

Interventions for Preventing Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews & Meta-analyses					
Allida et al. 2020 **Australia** **Cochrane review**	Using the Cochrane RoB tool, the percentage of trials at low or unclear risk of bias were: Selection bias (random allocation) 100%; selection bias (concealed allocation) 80%; performance bias (blinding of participants/personnel) 70%; detection bias (blinding of outcome assessor) 85%; attrition bias (incomplete reporting of data) 45%; and reporting bias (selective reporting) 95%	19 RCTs (21 interventions), including 1,771 participants recovering from stroke without depression at study entry. The mean age ranged from 55 to 73 years. Time since stroke ranged from 3 days to 6 months.	Trials compared pharmacological intervention vs. placebo (n=12, 14 interventions), psychological therapy) vs. usual care (n=7) non-invasive brain stimulation (NIBS) vs. placebo (n=0), and combinations of the above-mentioned interventions (n=0) Pharmacological agents included serotonin reuptake inhibitor (SSRI, n=6), a tricyclic antidepressant (n=1), serotonin-norepinephrine reuptake inhibitor against placebo (SRNI, n=1), serotonin receptor antagonists and reuptake inhibitors (SARIs, n=1). Other treatments were used in 5 trials. Duration of therapy ranged from 1 to 12 months. Psychological therapy included problem solving or cognitive behavioral therapy, with therapy provided from one visit per week x 4 weeks to monthly home visits over one year.	**Primary outcomes:** Risk of depression (using trial criteria) at the end of treatment, scoring above cut-off points for a depressive disorder **Secondary outcomes:** Depression scores, psychological distress, cognition, ADL, adverse events (death)	*Antidepressants vs. placebo* Antidepressants significantly reduced the risk of depression (RR=0.50, 95% CI 0.37 to 0.68, 9 trials, n=734; GRADE: very low) Insufficient data for pooling results for co-primary outcome Antidepressants were not associated with significantly better Hamilton Depression Rating Scale scores (MD=0.59, 95% CI -1.46 to 2.63, 4 trials, n=100; GRADE: very low) or Barthel Index scores (MD=-3.86, 95% CI -9.48 to 1.77, 3 trials, n=116; GRADE: very low). The risk of death was not increased significantly with antidepressants (RR=1.25, 95% CI 0.32 to 4.91, 9 trials, n=496; GRADE: very low). *Psychological therapy vs. usual care* Therapy was associated with a significantly lower risk of depression (RR=0.68, 95% CI 0.49 to 0.94, 2 trials, n=607; GRADE: very low). The risk of death was not increased significantly with therapy (RR=1.18, 95% CI 0.73 to 1.91, 5 trials, n=975; GRADE: very low).
Salter et al. 2012	N/A	8 RCTs trials that examined prevention of post-stroke	All trials were placebo controlled. Classes of	**Primary outcome:** The development of	Interview-based assessments were used to determine the presence/absence of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **Systematic Review**		depression (PSD) via comparison of pharmacotherapy with a control condition. Participants were limited to individuals with no clinically diagnosable PSD at study entry.	active agents examined included SSRIs, tricyclic antidepressants, tetracyclic antidepressants and atypical antidepressants	PSD at the end of treatment.	depression in all studies except one that used the HADS. Pooled analysis, based on 776 observations, demonstrated a significantly reduced risk for development of PSD associated with the use of prophylactic pharmacotherapy (OR=0.34, 95% 0.22-0.53, p<0.001). In a sensitivity analysis, including the 5 trials with treatment duration of 1 years, there was a significant reduction in odds for PSD (OR=0.31, 95% CI 0.18, 0.56; p<0.001). The most commonly reported side effects, when reported were tiredness/fatigue, dizziness and gastrointestinal upsets (most often nausea and diarrhea).
Yi et al. 2010 **China** **Systematic Review**	NA	6 trials (3 English, 3 Chinese) including study participants confirmed as having no diagnosis of depression following stroke, at study entry.	Trials compared the use of fluoxetine in the prevention of post-stroke depression (PSD) vs. placebo (n=3) or no treatment conditions (n=3). Duration of intervention ranged from 4 to 12 weeks.	**Primary outcome:** Incidence of PSD	Only 3 studies provided data on the development of new onset depression in treatment vs. control conditions (n=176). Treatment with fluoxetine was associated with a significantly reduced risk of the development of PSD (OR=0.25, 95% CI 0.11-0.56, p=0.0009). Analysis of symptom severity suggested that active treatment was associated with a non-significant reduction in symptoms (WMD=-3.97, 95% CI-9.85-1.9). Drop-out rates attributable to adverse events ranged from 0% to 11.1% in groups assigned to fluoxetine treatment and 0% to 14.3% in comparison groups. Drop-out rates were similar between groups
Pharmacotherapy					
Mikami et al. 2014	CA: ☑ Blinding:	176 patients from Robinson et al. 2008. (27 with generalized anxiety disorder identified at	As per Robinson et al. 2008.	**Primary outcome:** Risk of developing generalized anxiety	At the end of 12 months, there were 9 cases of GAD in patients who received placebo vs. 2 cases for those who received escitalopram

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **RCT**	Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	baseline, were excluded from the current analysis). 149 patients were aged 50-90 years recovering from ischemic or haemorrhagic stroke occurring within the previous 3 months, who were not diagnosed with depression or anxiety.	Patients were randomly assigned to receive 1 of 3 treatments: i) escitalopram 10 mg/d (if <65 yrs, 5 mg/d for patients ≥ 65, n=59) ii) matching placebo, n=58 or iii) problem-solving therapy (PST), n=59, (6 treatment sessions over 12 weeks + 6 reinforcement sessions over 9 months). The problem-solving therapy used in this study was a manual-based intervention developed in the UK. All sessions were videotaped and evaluated for adherence.	disorder (GAD), adjusting for age, gender, previous history of GAD and FIM	and 3 who received PST. Compared with escitalopram, patients who received placebo were significantly more likely to develop GAD (HR=4.95, 95% CI 1.54-15.93, p=0.007). Compared with PST, patients who received placebo were significantly more likely to develop GAD (HR=4.00, 95% CI 1.84-8.7, p=0.0005). There were 7 patients with GAD and comorbid depression. There were 7 patients with GAD, but without depression. There were 5 cases of GAD (- depression) in patients who received placebo vs. 0 cases for those who received escitalopram and 2 who received PST. After combining the results from the 2 active treatment arms, the risk of developing GAD was significantly higher for patients who received placebo (HR=6.63, 95% CI 2.85-15.4, p<0.0001).
Zhang et al. 2013 **China** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	95 patients, aged 40-80 years, admitted to a neurology unit following acute ischemic stroke, without a psychiatric disorder. Mean age was 64 years, 55% were male.	Following a comprehensive assessment battery, participants were randomly assigned to receive either treatment with duloxetine (30 – 90 mg/day; n=49) or a placebo (n=48) for 12 weeks, in addition to routine therapy.	**Primary outcome:** Minor and major depression, defined as scores of 8-17 (minor) and >17 (major) using the Hamilton Depression Scale (HDS) **Secondary outcomes:** Changes in scores from baseline to 24 weeks) in HDS, NIHSS, MMSE, the ADL (Chinese version) and SF-36	The incidences of minor and major depression were significantly lower in the duloxetine group (28.6 vs. 12.5%, p=0.05 and 24.5 vs. 8.3%, p<0.05, respectively). At 24 weeks, the use of duloxetine was associated with significantly improved scores on all other assessments. There were 21 dropouts (n=12 duloxetine, n=9 control). Nausea and vomiting were the most commonly-reported side-effects.
Chollet et al. 2011	CA: ☑	118 patients aged 18-85 years, free from clinical depression	Participants were randomized 1:1, 5-10	**Primary outcome:** FMMS scores at day 90	The incidence of depression was significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
France **RCT** ***Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)***	Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	and not taking any anti-depressant medication enrolled within 5 to 10 days of stroke with Fugl-Meyer Motor Scale (FMMS) scores of <55. Mean age was 65 years, 61% were men.	days post-stroke to receive fluoxetine (20 mg/day) or placebo for 90 days. All participants received physiotherapy and standard inpatient stroke care during the study period.	(results reported below). **Secondary outcomes:** NIHSS, modified Rankin Scale, and the Montgomery Asberg Depression Ration Scale at 90 days.	lower in the fluoxetine group (7% vs. 29%) Over the treatment period, there was no change in depressive symptomatology within the treatment group (adjusted mean change = -0.1, 95% CI -2.1 to 1.9) while there was a significant increase in symptoms in the placebo group (adj. Mean change = 3.2, 95% CI 1.1-5.3, p=0.032). Two serious adverse events occurred in the fluoxetine group (hyponatraemia and partial seizure). Transient digestive disorders (nausea, diarrhoea, and abdominal pain) were more common in the active treatment group (25% vs. 11%).
Tsai et al. 2011 **Taiwan** **RCT**	CA:☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	92 patients admitted to a neurology unit following first or recurrent ischemic stroke (within the preceding 4 weeks) and no depression. Individuals with previous depression, those taking antidepressants or with possible, undiagnosed depression (HAM-D≥10) were excluded from the study	Study participants were randomized to receive either 50 mg milnacipran (titrated to 100 mg by one week of treatment) per day, or matching placebo for 1 year.	**Primary outcome:** Incidence of post-stroke depression (PSD), diagnosed using DSM IV criteria.	56 participants (60.9%) completed the study. Overall, 8 participants developed PSD during the treatment period – only one of whom was assigned to the active treatment condition. The incidence of PSD was significantly lower in the treatment group (2.2% vs. 15.2%, p=0.048). Side effects were reported by both groups – there was no significant between group difference reported for study withdrawal due to side effects (p=0.73). The main reason for study withdrawal was reported to be difficulty in following the study protocol, not side effects associated with treatment. In total, 7/21 patients who withdrew from the active treatment group did so because of reported side effects.
Robinson et al. 2008, 2017 **Mikami et al. 2011** **USA**	CA:☑ Blinding: Patient ☒ Therapist ☒ Assessor ☑	176 patients aged 50-90 years recovering from ischemic or haemorrhagic stroke occurring within the previous 3 months, who were not diagnosed with depression. Depression was	Patients were randomly assigned to receive 1 of 3 treatments: i) escitalopram 10 mg/d (if <65 yrs, 5 mg/d for patients ≥ 65, n=59) ii) matching	**Primary outcome:** The onset of diagnosable major or minor depression, diagnosed using DSM-IV criteria at 12 months.	At one year, in the per-protocol analysis, adjusted for previous history of mood disorders, patients assigned to the placebo condition were more likely to develop depression than individuals receiving either therapy with escitalopram (adj. HR= 4.5, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	ITT:☑	assessed using the DSM-IV criteria or a score >11 on the Hamilton Depression Scale. Mean ages across treatment groups ranged from 61-97 years, 59.7% of participants were male.	placebo, n=58 or iii) problem-solving therapy (PST), n=59, (6 treatment sessions over 12 weeks + 6 reinforcement sessions over 9 months). The problem-solving therapy used in this study was a manual-based intervention developed in the UK. All sessions were videotaped and evaluated for adherence.	**Secondary outcomes:** FIM, neuropsychological tests Assessments were conducted at 3, 6, 9 and 12 months.	CI 2.4-8.2, p<0.001; or problem-solving therapy (adj. HR=2.2, 95% CI 1.4-3.5, p<0.001). The results were similar in the intention-to-treat analysis that included 27 patients who did not receive any treatment. Escitalopram was superior to placebo (23.1% vs. 34.5%, HR = 2.2 95% CI 1.2-39, p=0.007); however, problem-solving therapy was not (30.5% vs. 34.5%, HR=1.1, 95% CI 0.8-1.5, p=0.51). All patients experienced improvement in ADLs over time, but there were no significant time x treatment group interactions. There were no between group differences for any of the adverse events reported (decreased libido, fatigue, and GI symptoms). There was no evidence that patients receiving problem-solving therapy were more or less likely to be hospitalized with illness of cardiovascular origin than individuals receiving escitalopram. **2011 follow-up study** During the 6 months after cessation of treatment, 108 participants were available for evaluation. The incidence of new onset major depression was significantly higher for participants initially randomized to receive escitalopram (4 cases (11.8%) vs. 0 for placebo (p=0.114) and 0 for PST (p=0.038). Mean Hamilton Depression Scale scores were significantly higher for patients who received escitalopram compared with those

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					who received placebo or PST (6.8 vs. 4.5 or 4.0, p=0.007, respectively). **2017 follow-up** A mean of 8 years following the end of treatment, 122 participants were available. Participants who received PST were significantly less likely to have died (HR= 0.4625), compared with the combined group of escitalopram + placebo. Increasing age and the development of depression were significant predictors or mortality.
Almeida et al. 2006 **Australia** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	111 patients recovering from acute stroke (within previous 2 week) without severe cognitive impairment, aphasia or depression. Mean age was 67.5 years, 65% were male. Mean baseline Hospital Anxiety & Depression Scale (HADS-D) score was 3.2	Participants were randomly assigned 1:1 to receive treatment with sertraline (50 mg/day) or a matching placebo for 24 weeks.	**Primary outcome:** Development of significant symptoms of depression (HADS-D≥8 or diagnosed through clinical examination) at 24 weeks **Secondary outcomes:** Changes in HADS-D, MMSE and mRS scores at 24 and 52 weeks	At 24 weeks, 21.6% of patients assigned to the placebo group and 16.7% of patients assigned to treatment with sertraline were diagnosed with depression (OR = 0.8, 95% CI 0.3-2.1, p=0.59). Trial medication was stopped in 51.8% (placebo) and 47.3% (sertraline), mostly due to reported side effects. At 52 weeks, 30% in the placebo group vs. 22.7% in the active treatment group met the criteria for depression (p=0.43). There were no significant differences in scores on any of the secondary outcomes, assessed at either 24 or 52 weeks.
Rasmussen et al. 2003 **Denmark** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	137 patients admitted to the neurology units of a hospital system following stroke that occurred within the preceding 4 weeks, without depression. Individuals with significant aphasia or cognitive impairments (dementia) were excluded. Mean age was 70 years, 60% were men.	Participant were randomly assigned to treatment with sertraline (a maximum dose of 150 mg/day/, n=70) or matching placebo (n=67) for a period of one year.	**Primary outcome:** Development of depression, diagnosed as a score >18 on the Hamilton Depression Scale (HDS-D)-17, or ≥9 on the HDS-6, or >16 on the Geriatric Depression Scale (GDS)	At baseline the mean HDS-17 was significantly higher in the placebo-treated group (7.6 vs. 6.5, p<0.05). After 52 weeks, a significantly lower number of patients treated with sertraline developed depression, based on HAD-17 criteria (8.2% vs. 22.8%, p<0.05). Treatment superiority was evident after 21 weeks. Treatment with sertraline was also

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					significantly more effective in preventing depression, assessed using HDS-6 criteria. (11.5% vs. 28.1%, p<0.05). Treatment superiority was evident after 6 weeks. Treatment with sertraline was also significantly more effective in preventing depression, assessed using GDS criteria, where treatment superiority was evident after 20 weeks. There were no significant differences between groups in terms of the frequency of reported effects. There were fewer patients in the active treatment group who reported severe cardiovascular and noncardiovascular events. Incidence of diarrhea and nausea were 5% higher among individuals treated with sertraline.
Non-pharmacological Interventions					
Hackett et al. 2013 **Australia** **RCT** ***ImProving Outcomes after STroke (POST)***	CA: ☑ Blinding patient: ☒ therapist ☒ assessor: ☑ ITT: ☑	201 patients, aged ≥18 years, with a recent stroke (onset within the previous 8 weeks), with a Hospital Anxiety and Depression Scale (HADS) score <8. Patients with serious concomitant illness, were excluded. Mean age was 70 years, 43% were female, 28% were independent in ADLs.	Participants were to the intervention group (n=100) or to the usual care control group (n=101). Participants in the intervention group received a personalized post card at 1, 2, 3, 4, and 5 months following hospital discharge.	**Primary outcome:** Presence of depression at six months, defined as HADS>8. **Secondary outcomes:** Changes in HADS-D, HAD-A and PHQ-9, between 3 and 6 months	The proportion of participants with depression at the end of the 6-month study period did not differ significantly between the two groups (1.1% vs. 3.9%; RR= 0.29, 95% CI 0.03 to 2.71). Additionally, no significant between group differences were reported with respect to mean scores on the HADS total and subscale scores or on the PHQ-9.

Treatment of Other Mood States

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Post-stroke Anxiety					
Chun et al. 2018 **UK** **Systematic review & meta-analysis**	6 trials were at high risk of bias	14 RCTs (19 comparisons) including 928 participants with stroke (n=12) and stroke +/- traumatic brain injury (n=2). The mean age ranged from 48 to 72 years in studies of stroke patients only, and from 35 to 58 years in the two studies that included TBI patients. There were more men than women in all trials. In 7 trials, a baseline diagnosis of anxiety disorder or 'emotional distress' was an eligibility requirement. In 6 trials, a baseline anxiety level for inclusion was not specified. Time from stroke to intervention ranged from 2 weeks to 6 years in the 8 trials that reported this	Trials compared psychotherapy (motivational interviewing, cognitive behavioral therapy, psychotherapy, problem-solving, coping skills and self-management, paroxetine, imipramine, buspirone, and escitalopram n=8), pharmacotherapy (n=5), pharmacotherapy + psychotherapy (n=1), exercise therapy (yoga and resistance training, n=2) and other interventions (forest therapy, relaxation CD and acupuncture, n=3). The most common control conditions included placebo, usual care, and waitlist control	**Primary outcome:** Anxiety (timing of assessment not reported-assumed to be end of treatment)	Psychotherapy interventions were associated with a significant reduction in anxiety scores (SMD= −0.41, 95% CI -0.79 to −0.03, 6 trials). Pharmacotherapy was associated with a significant reduction in anxiety scores (SMD= −2.12, 95% CI -3.05 to -1.18, 4 trials). Pooled analyses were not conducted for the other interventions.
Knapp et al. 2017 **UK** **Cochrane Review**	Using the Cochrane RoB tool, one trial was at low risk of selection bias (randomization) and one trial was at low risk of attrition bias (incomplete outcome data). All trials were at high or unclear risk of bias for all	3 RCTs (n-196) including participants recovering from stroke who had been given a diagnosis of co-morbid depression and anxiety. Mean ages ranged from 59 to 68 years, 50%-64% were men.	In trial one, patients were randomly assigned to treatment with paroxetine, paroxetine + psychotherapy or usual care. In trial two, patients were assigned to receive either buspirone hydrocholoride or usual care, and in trial 3, patients received 4-week use of a relaxation CD (Golding et al. 2016).	**Primary outcomes:** Proportion of patients, following treatment, without a clinical diagnosis of anxiety based on the DSM (or other standard classification) and the proportion of patients scoring outside the symptom range as defined by the primary study author via anxiety rating scale or self-report.	Trial 1: Based on Hamilton-Anxiety Rating scores (HAM-A), mean anxiety scores were significantly lower in both intervention groups when compared to the control group at 6 weeks ($p<0.01$). A similar trend was noted for depression scale scores. Mean HAM-A scores were reduced by 58% in the paroxetine condition and 71% in the paroxetine + psychotherapy condition. Trial 2: At the four-week assessment point, both groups had experienced a reduction in HAM-A anxiety scores. However, reduction in anxiety was significantly greater in the intervention group when compared to the usual care group ($p<0.01$). Treatment was

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	other domains.				also associated with a significant reduction in depressive symptoms. There was no information available regarding the treatment of anxiety only. Trial 3: 4/10 participants in the intervention group were no longer considered to have clinical levels of anxiety at three months, vs. 1/10 participant in the control group
Golding et al. 2016, 2017 **UK** **RCT**	CA: ☑ Blinding patient: ☒ therapist ☒ assessor: ☑ ITT: ☒	21 persons living in the community, recovering from stroke, with Hospital Anxiety and Depression (HADS)-A score ≥6, who were cognitively intact. Mean age was 65 years, 50% were female. Mean time since stroke was 118 months (intervention group) and 69.9 months (control group).	Participants were randomized 1:1 to an intervention or control group. Persons in the intervention group received a self-help CD, with instructions to listen to it and following its instructions 5x/week for a month, at which point they could choose whether to continue using the CD. Persons in the control group received the CD after 3 months.	**Primary outcome:** Changes in HADS-A scores, from baseline to 1, 2 and 3 months	At baseline, the mean HADS-A scores for participants in the intervention and control groups were 10.9 and 10.5, respectively. At one month, mean HADS-A scores were significantly lower in the intervention group (7.4 vs. 10.6, Δ=3.5 vs. -0.10, p=0.002). At 2 months, mean HADS-A scores were significantly lower in the intervention group (7.0 vs. 11.4, Δ=4.11 vs. -0.90, p<0.001). At 3 months, mean HADS-A scores were significantly lower in the intervention group (6.9 vs. 11.0, Δ=4.22 vs. -0.50, p=0.001). At 3 months 4 participants in the intervention group no longer had clinical signs of anxiety vs. 1 in the control group. **One-year follow-up** 15 participants completed one-year assessments. Mean HADS-A scores were significantly lower at one year, from baseline for participants in the intervention group (4.43 and 9.14, p=0.001), but not significantly lower from at one year from post-intervention.
Post-Stroke Apathy					
Tan et al. 2022	5 of the included trials	8 RCTs including 334 patients with neurological	Trials examined nonpharmacological	**Primary outcome:** Apathy Evaluation	Compared with the control condition, non-pharmacological interventions were

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
China **Network meta-analysis**	were at overall high risk of bias using the Cochrane RoB tool.	conditions (dementia or mild cognitive impairment, n=7 and stroke n=1). All participants were hospitalized or residents of a nursing home, except in one trial where a portion of participants resided at home). Mean ages ranged from 65 to 82 years. No indicators of baseline apathy status (+/-) are provided.	interventions including (rTMS, n=2) music therapy (n=1), cognitive therapy (n=3), and occupational therapy (n=2). The control groups were sham rTMS and usual care. Duration of the intervention lasted from 2 weeks to 10 months.	Scale	associated with a significant reduction in AES scores in pooled analysis, combining all trials (MD=-6.88, 95% CI −8.50 to −5.26). In direct comparisons with the control condition, all interventions except music therapy were associated with significant reductions in AES scores. Mean differences ranged from -8.25 to cognitive rehabilitation to -4.87 for occupational therapy. In head-to-head comparisons, no active intervention was superior to another. In order of superiority of active treatments were rTMS, cognitive intervention, occupational therapy, and music therapy.
Starkstein et al. 2016 **Australia** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	13 patients (out of 20 eligible) aged ≥40 and <90 years, who had sustained a recent stroke and met the criteria for apathy 8 weeks later (based on a score of ≥14 on the Apathy Scale), without depression, dementia, or severe aphasia. Mean age was 69 years, 77% were male.	13 participants were randomized to receive 900 mg nefiracetam (n=6) or placebo (n=7) daily for 12 weeks.	**Primary outcomes:** Change in Apathy Scale (AS) scores at 12 weeks	Mean AS scores at baseline were 23.0 (placebo) and 20.5 (nefiracetam), p=0.42. At 12 weeks, the mean changes in AS scores were -7.6 (placebo) and -6.3 (nefiracetam), Δ=1.2, 95% CI -14.8-17.2), which was not significantly different. There were 4 2 cases of severe adverse events in the placebo group vs. 5 in the nefiracetam group.
Robinson et al. 2009 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☑	70/159 patients diagnosed with major depression who completed 12 weeks of treatment with nefiracetam (Robinson et al. 2008), who also met the criteria for apathy (based on Apathy Scale scores). Mean ages were 64.7, 63.9 and 70.5 in the placebo and 2 treatment groups,	Participants were randomly assigned to receive 1 of 3 treatments for 12 weeks: i) 600 mg nefiracetam (n=26), ii) 900 mg nefiracetam (n=22) or iii) matching placebo.	**Primary outcome:** Change in Apathy Scale scores **Secondary outcome:** Apathy remission, defined as a 75% reduction in Apathy Scale scores	Mean baseline Apathy Scale scores across groups were 19.3, 20.3 and 21.2. Patients receiving 900 mg/day of nefiracetam showed a significantly greater decrease in Apathy Scale scores during the 12-week trial compared to patients receiving placebo (p<0.01). Patients receiving 600 mg/day of nefiracetam did not show a significantly greater decrease

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		respectively. 53.5% were female. There were no significant between group differences noted at baseline.			in Apathy Scale scores during the 12-week trial compared to patients receiving placebo (p=0.29). Remission was achieved by 4/22 patients in the 900 mg group, 1/26 patients in the 600 mg group and 0/22 in the placebo group (p=0.031).
Post Stroke Emotionalism					
Allida et al. 2022 **UK** **Cochrane review**	Using the Cochrane RoB too, all trials were at low or unclear risk of bias across all domains except for one trial in which the risk of bias due to incomplete reporting was high	7 RCTs published from 1989 to 2006, including 239 participants with emotionalism post stroke. The mean/median age ranged from 57.8 to 73 years.	Trials compared antidepressants (SSRIs, n=5, TCAs, n=2) vs. placebo. The duration of treatment ranged from 10 to 182 days.	**Primary outcome:** Emotionalism **Secondary outcomes:** Depression, cognitive functioning, ADL performance, adverse events	Fluoxetine (20 mg/day for 10 days) was associated with a ≥50% reduction in emotionalism, (RR=0.26, 95% CI 0.09 to 0.77, 1 trial, n=19; GRADE: very low), and a significant reduction in tearfulness (RR=0.32, 95% CI 0.12 to 0.86, 3 trials, n=163; GRADE: moderate) Sertraline was not associated with significantly greater improvement on Center for Neurologic Study - Lability Scale score (RR= 0.20, 95% CI 0.03 to 1.50, 1 trial, n=28; GRADE: low). Pharmacological agents were not associated with significant differences between groups for any of the secondary outcomes.

Abbreviations

CA: concealed allocation	CI: confidence interval	HADS; Hospital Anxiety & Depression Scale
HR: hazard ratio	ITT: intention-to-treat	MD: mean difference
mRS: modified Rankin Scale	NA: not assessed	NIHSS: National Institutes of Health Stroke Scale
OR: odds ratio	RoB: risk of bias	RR: relative risk
rTMS: repetitive transcranial magnetic stimulation	SMD: standardized mean difference	SSRI: selective serotonin reuptake inhibitor

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