HEART & STROKE FOUNDATION | CANADIAN Stroke BEST PRACTICE RECOMMENDATIONS

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Mood, Cognition and Fatigue Following Stroke

Evidence Tables

Post-Stroke Depression: Pharmacotherapy and Combined Treatment

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Mood, Cognition and Fatigue Writing Group

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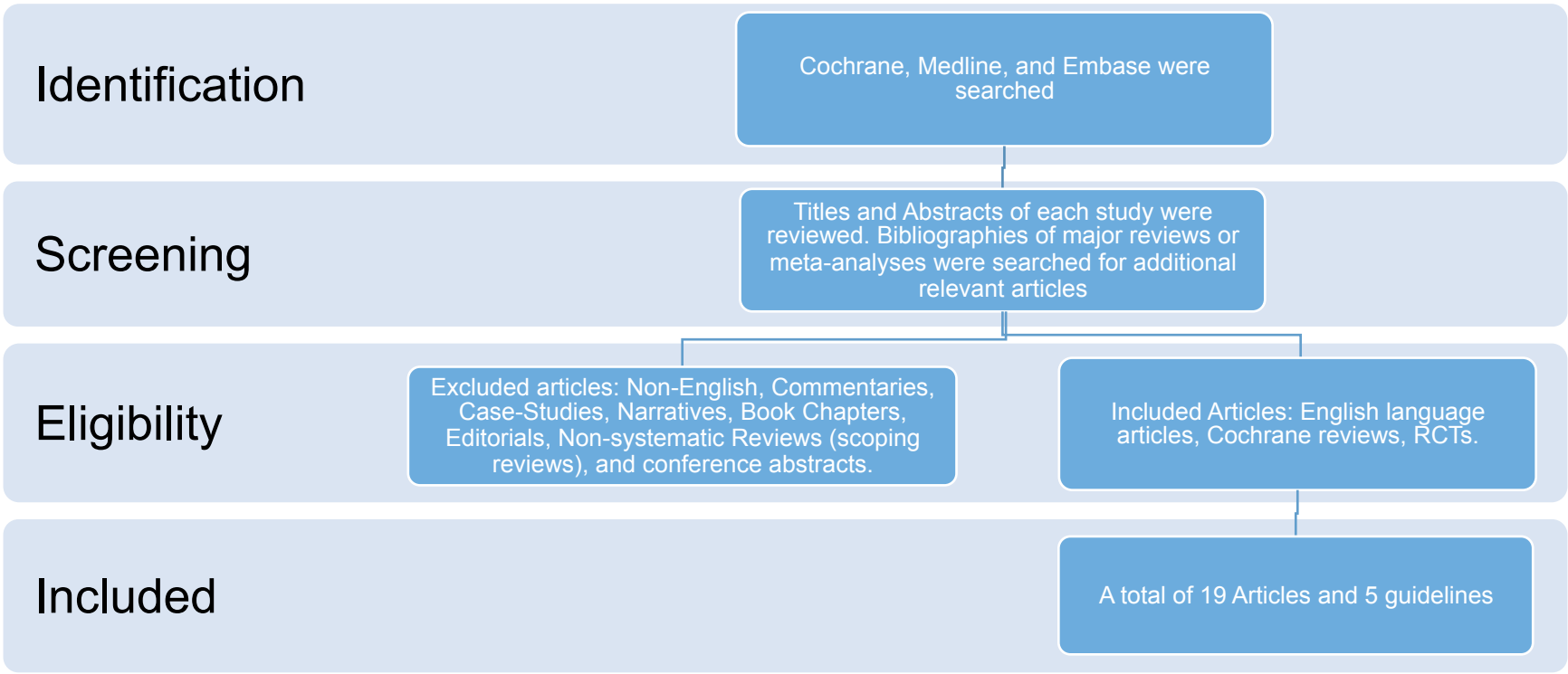
Search Strategy



The Medline, Embase, PsycInfo, and Cochrane databases were searched using the terms [stroke OR cerebrovascular disorders] and [depression OR depressive disorders OR anxiety OR anxiety disorders OR emotional incontinence]. 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 19 articles and 5 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010 Recommendations. Melbourne Australia.	**Mood disturbance** 1. All patients should be screened for depression using a validated tool (GPP) 2. Patients with suspected altered mood (e.g., depression, anxiety, emotional lability) should be assessed by trained personnel using a standardized and validated scale (B) 3. Diagnosis should only be made following clinical interview (GPP) 4. Psychological strategies (e.g., problem solving, motivational interviewing), can be used to prevent depression after stroke (B). 5. Routine use of antidepressants to prevent post-stroke depression is NOT recommended (B). 6. Antidepressants can be used for stroke patients who are depressed (following due consideration of the benefit and risk profile for the individual) and for those with emotional lability (B). 7. Psychological (cognitive-behavioural) intervention can be used for stroke patients who are depressed (B). **Behavioural change** 1. The impact of chronic behavioural changes (irritability, aggression, perseveration, adynamia/apathy, emotional lability, disinhibition, and impulsivity) on functional activities, participation and quality of life, including the impact on relationships, employment and leisure, should be assessed and addressed as appropriate over time (GPP). 2. Stroke survivors and their families/cares should be given access to individually tailored interventions for personality and behavioural changes e.g. participation in anger-management therapy and rehabilitation training and support in management of complex and challenging behaviour (GPP). **Care after hospital discharge** Stroke survivors can be managed using a care management model after discharge. If used, care manages should be able to recognize and manage depression and help to coordinate appropriate interventions via a medical practitioner (C).
Intercollegiate Stroke Working Party. National clinical guideline for stroke, 4th edition. London: Royal College of Physicians, 2012.	**Depression and anxiety** 1. Any patient considered to have depression or anxiety should be assessed for other mood disorders. 2. Patients with mild or moderate symptoms of depression should be given information, support and advice (see recommendation 6.34.1G) and considered for one or more of the following interventions: • increased social interaction • increased exercise • goal setting • other psychosocial interventions. 3. Patients prescribed antidepressant drug treatment for depression or anxiety should be monitored for known adverse effects, and treatment continued for at least 4 months beyond initial recovery. If the patient's mood has not improved 2–4 weeks after initiating treatment, check that the patient is taking the medicine as prescribed. If they are, then consider increasing the dose or changing to another antidepressant. 4. Patients receiving drug treatment for depression or anxiety should have it reviewed regularly to assess continued need. 5. Brief, structured psychological therapy should be considered for patients with depression. Therapy will need to be adapted for use in those with neurological conditions.

Guideline	Recommendations
	6. Antidepressant treatment should not be used routinely to prevent the onset of depression. **Emotionalism** 1. Any patient who persistently cries or laughs in unexpected situations or who is upset by their fluctuating emotional state should be assessed by a specialist or member of the stroke team trained in the assessment of emotionalism. 2. Any patient diagnosed with emotionalism should, when they show increased emotional behaviour, be appropriately distracted from the provoking stimuli. 3. Patients with severe, persistent or troublesome emotionalism should be given antidepressant drug treatment, monitoring the frequency of crying to check effectiveness. Patients should be monitored for known adverse effects. If the emotionalism has not improved 2–4 weeks after initiating treatment, check that the patient is taking the medicine as prescribed. If they are, then consider increasing the dose or changing to another antidepressant. **Psychological Care** 1. Services should adopt a comprehensive approach to the delivery of psychological care after stroke, which should be delivered by using a 'stepped care' model from the acute stage to long-term management (see chapter 7). 2. Interventions for individual disorders of mood or cognition should be applied within the framework of a stepped care and comprehensive model. 3. Patients with continuing disorders should be considered for comprehensive interventions tailored towards developing compensatory behaviours and the learning of adaptive skills. 4. Within Step 1 care all patients after stroke should be screened within 6 weeks of diagnosis, using a validated tool, to identify mood disturbance and cognitive impairment. 5. Assessment measures should be adapted for use with patients with expressive or minor receptive aphasia. In patients with more severe aphasia, an assessment tool designed specifically for this purpose, such as the SAD-Q or DISCS, should be used. In patients with aphasia or other impairments that complicate assessment, careful observations over time (including response to a trial of antidepressant medication if considered necessary) should be used. 6. Within Step 2 care, patients identified as having symptoms of mood disorder should be offered a more detailed assessment, seeking information on past history, potential causes and impact, and treatment preferences. 7. In patients with mild or moderate symptoms of mood disorder, patients and carers should be provided with information, support and advice about the mood disorder as the first line of intervention. This may be from within the MDT by nominated staff who are suitably trained and supervised, and may also involve the voluntary sector. 8. Within Step 3 care, patients with severe or persistent symptoms of mood disorder should be considered for referral to a specialist in the management of mood disorder in stroke. 9. Psychological or pharmaceutical treatment (or a combination) for mood disorder should be provided if: recommended by a clinician with expertise in managing mood disorder after stroke; or, as the second line of intervention, if the patient has not responded to information, support and advice. Any treatment should be monitored for effectiveness and kept under review. 10. Any patient assessed as having a cognitive impairment should be considered for referral to a specialist in cognitive aspects of stroke. Patients identified as having cognitive impairment or mood disorder should be reassessed before discharge decisions are taken.
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients	**Preventing post-stroke depression** 1. Routine prescription of antidepressants is not recommended to prevent post-stroke depression (B).

Guideline	Recommendations
with stroke: Rehabilitation, prevention and management of complications, and discharge planning: A national clinical guideline, 2010. Edinburgh, Scotland.	2. Offering routine psychological therapies in one-to-one format following a stroke is not recommended to prevent post-stroke depression (B). 3. Psychological principles from motivational interviewing and problem solving should be incorporated into education programmes for people who have had a stroke (B). 4. Stroke rehabilitation services should consider structured, psychologically-based programmes (incorporating education and advice) to target individuals' emotional adjustment to the impact of stroke, and to increase their sense of control over their recovery. Such programmes require staff training and ongoing evaluation to ensure clinical benefit (GPP). **Treating post-stroke depression** 1. Patients with post-stroke depression should be considered for antidepressant treatment, with decisions made on an individual basis. Clinicians should monitor response to treatment, plan regular reviews and should be vigilant to the possible occurrence of unwanted side effects, issues of adherence to medication and the possibility of symptom relapse (A). 2. Clinicians need to make decisions on the choice of antidepressant on a case-by-case basis, taking into account factors such as risk of seizures, falls and delirium (GPP). 3. Patients who fail to respond to antidepressant therapy, or who do not wish to take medication, should be considered for a trial of talking-based therapy, with clinicians carefully monitoring response to treatment (GPP). 4. Clinicians should be aware that environmental factors (eg opportunities for social interaction, noise levels) often have an impact on mood, and should consider whether it is possible to alter these factors when individuals experience post-stroke depression (GPP). **Emotional lability** 1. Patients with post-stroke emotionalism may be considered for a course of antidepressant medication (B). 2. Possible side effects of antidepressant treatment should be explained to patients prior to commencing treatment (GPP). 3. Patients and carers should be offered a clear explanation and advice about emotionalism, and considered for psychological (talking-based) support if they have a poor response to antidepressant medication and show evidence of distress about their condition. Local psychological support, education and advice should be considered on an individual basis as available. Such advice should be embedded in general education programmes. **Post-stroke emotional adjustment** 1. People who have had a stroke should be considered for workbook approaches that aim to address their beliefs and attitudes about their recovery (GPP). **Summary of Recommendations** 1. Appropriate referral to health and clinical psychology services should be considered for patients and carers to promote good recovery/adaptation and prevent and treat abnormal adaptation to the consequences of stroke (GPP). 2. All stroke patients (including those cared for in primary care) should be screened for mood disturbance (GPP). 3. Some form of screening should occur, eg using the Stroke Aphasic Depression Questionnaire (SAD-Q) or General Health Questionnaire of 12 items (GHQ-12): • as early as appropriate and definitely before discharge, and • at regular intervals thereafter

Guideline	Recommendations
	4. Clinical judgement should be used to determine how regularly mood should be re-assessed (GPP). If an individual is suspected of having a mood disorder they should be referred to an appropriately trained professional for a full assessment, or to a rehabilitation team member who has received training in the identification of psychological distress (GPP).
VA/DoD clinical practice guideline for the management of stroke rehabilitation 2010.	**Post stroke depression** 1. There are several treatment options for the patient with stroke and mild depression that can be used alone or in combination based on the patient's individual need and preference for services. Refer to VA/DoD guidelines for the management of Major Depression Disorder (MDD). 2. Patients diagnosed with moderate to severe depression after stroke should be referred to Mental Health specialty for evaluation and treatment. 3. There is conflicting evidence regarding the use of routine pharmacotherapy or psychotherapy to prevent depression or other mood disorders following stroke. 4. Patients with stroke who are suspected of wishing to harm themselves or others (suicidal or homicidal ideation) should be referred immediately to Mental Health for evaluation. 5. Recommend that patients with stroke should be given information, advice, and the opportunity to talk about the impact of the illness upon their lives. **Other Mood Disorders** 6. Patients following stroke exhibiting extreme emotional lability (i.e. pathological crying/tearfulness) should be given a trial of antidepressant medication, if no contraindication exists. SSRIs are recommended in this patient population. [A] 7. Patients with stroke who are diagnosed with anxiety related disorders should be evaluated for pharmacotherapy options. Consider psychotherapy intervention for anxiety and panic. Cognitive Behavioral Therapy has been found to be a more efficacious treatment for anxiety and panic disorder than other therapeutic interventions. 8. Recommend skills training regarding Activities of Daily Living (ADL's), and psychoeducation regarding stroke recovery with the family. 9. Encourage the patient with stroke to become involved in physical and/or other leisure activities. **Assessment of emotional and behavioral state** 1. Initial evaluation of the patient should include a psychosocial history that covers pre-morbid personality characteristics, psychological disorders, pre-morbid social roles, and level of available social support. 2. Brief, continual assessments of psychological adjustment should be conducted to quickly identify when new problems occur. These assessments should also include ongoing monitoring of suicidal ideation and substance abuse. Other psychological factors deserving attention include: level of insight, level of self-efficacy/locus of control, loss of identity concerns, social support, sexuality, and sleep. 3. Review all medications and supplements including over the counter (OTC) medications that may affect behavior and function. 4. Inclusion of collateral information (e.g., spouse, children) is recommended to obtain a comprehensive picture of the patient's pre-morbid functioning and psychological changes since the stroke. 5. There is insufficient evidence to recommend the use of any specific tools to assess psychological adjustment. Several screening and assessment tools exist. (See Appendix B for standard instruments for psychological assessment.) 6. Post-stroke patients should be assessed for other psychiatric illnesses, including anxiety, bipolar illness, SUD, and

Guideline	Recommendations
	nicotine dependence. Refer for further evaluation by mental health if indicated. **Use of standardized assessments** 1. Recommend that all patients should be screened for depression and motor, sensory, cognitive, communication, and swallowing deficits by appropriately trained clinicians, using standardized and valid screening tools. [C] If depression, or motor, sensory, cognitive, communication, or swallowing deficits are found on initial screening assessment, patients should be formally assessed by the appropriate clinician from the coordinated rehabilitation team. [C]
Duncan PW, Zorowitz R, Bates B, et al. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke 2005;36:e100-e143.	**Mood Disturbance** 1. The Working Group makes no recommendation for the use of any specific diagnostic tool over another. 2. Recommend using a structured inventory to assess specific psychiatric symptoms and monitor symptom change over time (refer to the VA/DoD Guideline for Management of Major Depressive Disorder at http://www.oqp.med.va.gov/cpg/MDD/MDD_Base.htm). 3. Recommend assessing poststroke patients for other psychiatric illnesses, including anxiety, bipolar illness, and pathological affect. 4. Strongly recommend that patients with a diagnosed depressive disorder be given a trial of antidepressant medication, if no contraindication exists. 5. The Working Group makes no recommendation for the use of 1 class of antidepressants over another; however, side effect profiles suggest that SSRIs may be favored in this patient population. 6. Recommend patients with severe, persistent, or troublesome tearfulness be given a trial on antidepressant medications. 7. Recommend SSRIs as the antidepressant of choice in patients with severe, persistent, or troublesome tearfulness. 8. There is insufficient evidence to recommend for or against the use of individual psychotherapy alone in the treatment of PSD. 9. Recommend patients be given information, advice, and the opportunity to talk about the impact of the illness on their lives. 10. Routine use of prophylactic antidepressants is not recommended in poststroke patients. 11. Recommend that mood disorders causing persistent distress or worsening disability be managed by, or with the advice of, an experienced clinical psychologist or psychiatrist. **The use of standardized assessment tools** 1. Recommend that all patients be screened for depression and motor, sensory, cognitive, communication, and swallowing deficits by appropriately trained clinicians, using standardized and valid screening tools. Recommend that if depression and motor, sensory, cognitive, communication, and swallowing deficits are found, all patients should be formally assessed by the appropriate clinician from the coordinated rehabilitation team.

Evidence Tables

Pharmacotherapy for Post-Stroke Depression

Meta-analyses examining the effectiveness of pharmacotherapy for the treatment of post-stroke depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Chen et al. 2006 **Systematic review and Meta-analysis**	N/A	16 RCTs representing 1320 stroke patients with a diagnosis of depression at baseline.	Included studies compared any single antidepressant with placebo, with no restrictions of inclusion based on study or patient characteristics.	Outcome measures included response rate, depression rating scale scores, and improvement in ADLs or neurologic impairment.	Treatment was associated with significant reduction in depressive symptomatology on all scales used to assess outcome, with a pooled RD = 0.23 (95% CI 0.03-0.43). Also, a relationship between duration and benefit of treatment was identified. Pooled analysis of studies with treatment durations of 1 and 2 weeks revealed no significant treatment effects; however, from 3 weeks onward, demonstrated effects were, generally, of increasing significance. Treatment was not found to have a significant impact on improvement in ADLs and Neurologic impairment.
Hackett et al. 2008 **Cochrane Review and Meta-analysis**	N/A	12 RCTs representing 1121 stroke patients with a diagnosis of depression at baseline.	Included studies compared any pharmacological agent with placebo. Trials investigating an agent for reasons other than treatment of depression were excluded.	Primary analyses investigated the prevalence of diagnosable depressive disorder following treatment. Secondary outcomes included depression rating scale scores, physical function, and mortality.	Pharmacotherapy was associated with a small, but significant, positive treatment effect in terms of treating depression (pooled OR = 0.47; 95% CI 0.22-0.98) and reducing depressive symptomatology (pooled OR = 0.22 (95% CI 0.09-0.52). However, in light of a significant increase in adverse events, including central nervous system and gastrointestinal events, the authors concluded that “more research is required before recommendation can be made about the routine use of such treatments” (pg 2).
Iovieno et al. 2011 **Systematic Review and Meta-analysis**	N/A	212 trials were identified for inclusion. 25 trials focussed on the treatment of individuals with MDD and a co-morbid Axis III disorder. Six trials were included that examined treatment in individuals with MDD + stroke.	Included double-blind RCTs trials of antidepressant monotherapy for major depressive disorder in populations with co-morbid Axis III diagnoses. Studies were identified from MEDLINE published	Primary outcome for the meta-analysis was clinical response defined as a ≥50% reduction in HRSD or MADRS score from baseline to study endpoint or a CGI <3 at the final visit. When multiple assessment tools were used, the HRSD was selected in order to	Overall, the use of antidepressant therapy was associated with higher response rates compared to placebo conditions in studies that included individuals with co-morbid Axis III disorders (RR=1.42, 95% CI 1.25, 1.6 p<0.0001). In addition, studies that examined depression following stroke demonstrated significantly higher response rates (56.1% vs. 42.1%) when compared to placebo (RR=1.43, 95% CI 1.05, 2.05 p=0.04). There was no evidence of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			from 1980 – 2009 inclusive. Reference lists of identified studies were handsearched for additional citations.	minimize assessment heterogeneity. ITT-based assessment rates were used in this analysis.	significant statistical heterogeneity associated with these analyses.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Andersen et al. 1994* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	66 adult stroke patients with moderate depression (defined as a baseline HRSD score of 13 and symptom duration of at least 2 weeks) 2 to 52 weeks after stroke.	Patients were assigned to receive the "recommended" dose of citalopram (20 mg p.o q hs for individuals less than 66 years of age and 10 mg p.o. qhs for individuals older than 66 years of age). Response was assessed at 6 weeks. For individuals assessed as non-responders (HRSD scores > 13) individuals were offered treatment with either nortriptyline or mianserin. For responders (HRSD scores < 13), treatment was continued (as per double-blind protocol) for an additional 10 weeks.	Outcome was assessed using the Hamilton Rating Scale for Depression and the Melancholia Scale at baseline, 1,3,6, 9, 12 and 16 weeks of treatment.	Significant improvement was noted on the Hamilton Rating Scale for Depression (HRSD) and the Melancholia Scale with citalopram when compared to placebo. Adverse Events: There was 1 death, 6 adverse events and 3 strokes noted by the authors.
Robinson et al. 2000* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑	104 adult individuals with previous stroke (within 6 months of study baseline). 48 individuals with no diagnosis of depression were enrolled in the study in	This study was originally designed as a randomized crossover trial. Patients were randomly assigned to either **fluoxetine**	The Hamilton Rating Scale for Depression (HRSD-28) was used to assess depression at baseline and at each 3-week evaluation point. Successful response	**ITT analysis**: Overall, there was a significant time X treatment interaction identified (F=3.45, df=8, p=0.004). Post hoc analysis of this interaction demonstrated no significant difference between the nortriptyline and fluoxetine treatment groups at baseline;

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	Assessor ☒ ITT: ☑	order to assess effects of antidepressant use on recovery.	(10mg/d gradually increased to 40 mg/day) or **nortriptyline** (dose of 25 mg/day gradually increased to 100 mg/day) or identical **placebo** given over 12 weeks. Patients received 12 weeks of active treatments and crossed-over to 12 weeks of placebo treatment. However, as data from a significant number of participants assigned to the placebo condition "became ineligible for analysis" (31% response rate), an independent groups design was applied to the analysis	to treatment was defined as a >50% reduction in the HRSD scale score + failure to fulfill the criteria for major or minor depression.	however, the placebo group appeared to have lower HRSD scores than the group assigned to treatment with nortriptyline ($p<0.05$). When the analysis was corrected for this difference, post hoc analysis demonstrated that individuals treated with nortriptyline had greater declines in HRSD scores than individuals treated with either fluoxetine or with placebo at 12 weeks follow-up. **Efficacy analysis**: Overall, at 12 weeks, there was a significant time X treatment interaction identified ($F=3.65$, $df=8$, $p=0.001$). Post hoc analysis demonstrated no between group differences on the initial evaluation; however, at 12 weeks, the nortriptyline group demonstrated lower HRSD scores than the fluoxetine group ($p<0.05$) as did the placebo group ($p<0.05$). The rate of successful treatment was 77% in the nortriptyline group, 14% in the fluoxetine group and 31% in the placebo condition. Neither depressed or non-depressed patients in either active treatment condition demonstrated significant greater improvement in functional recover than those assigned to placebo. Adverse events: weight loss (fluoxetine in elderly patients), anxiety, insomnia, GI symptoms
Wiart et al. 2000* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	31 patients with a recent (within 3 months) ischemic stroke and a diagnosis of major depressive disorder (ICD-10) and assessed using the MADRS. Patients with a history of multiple strokes, severe aphasia and/or cognitive impairment were excluded.	Participants were randomly assigned to receive treatment with either 20 mg fluoxetine (n=16) or matching placebo (n=15) for a period of 45 days.	After baseline assessment, changes in symptoms of depression were assessed at days 15, 30 and 45 using the MADRS. A clinical interview was also administered as well as a clinical examination, the Motricity Index, MMS and FIM.	Participants assigned to treatment with fluoxetine demonstrated greater improvement on MADRS scores than did individuals assigned to the placebo condition at the end of study (45 days) ($p=0.05$). In addition, response rates were greater in the fluoxetine group (62.5% vs. 33.3%). There were global improvements in function demonstrated by both groups (NS). Side effects: Side effects reported by individuals assigned to fluoxetine included, nausea, seizure, tremor, confusion, increased transaminases.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Fruehwald et al. 2003* **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	54 patients diagnosed with moderate to severe post-stroke depression were randomized within 2 weeks of stroke. Individuals with significant communication impairments or more than mild cognitive impairments were not included in the study.	Patients were randomly assigned to receive treatment with either fluoxetine (n=26) or matching placebo (n=24). Treatment was given in a single dose (20 – 40 mg) each morning. The treatment period lasted for 12 weeks. If at the 4 week evaluation, the participant did not demonstrate response (ie. HRSD >13), treatment was continued at a doubled dose, as per double-blind protocol for an additional 8 weeks.	Assessments undertaken included the HRSD, the MMSE, BI, BDI as well as the clinical global impression (CGI).	Analyses were per protocol. 50 patients completed the trial. At baseline, both groups demonstrated comparable severity of depressive symptomatology. Both groups demonstrated significant (within group) improvement over time and there was no significant difference in favour of fluoxetine in between group comparison at 4 weeks. However at 12 weeks, BDI score of patients treated with fluoxetine had decreased while, in the placebo group, scores increased. 18 months post-baseline, patients who had been assigned to treatment with fluoxetine were significantly less depressed than those who had been assigned to the placebo condition. Side effects: No major effects were reported. Minor effects reported by participants included dizziness, nausea and cephalalgia.
Murray et al. 2002* **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)	Individual participants were assigned to either the treatment or placebo conditions. 62 patients received sertraline (50 – 100 mg/day) and 61 received a matching placebo.	Primary study outcome was change in MADRS score from baseline to weeks 6 and 26.	Both groups demonstrated significant improvements. No significant between group differences were demonstrated on the primary study outcomes for individuals diagnosed with major vs. minor depression. There was a significant between-group difference favouring treatment with sertraline identified via assessments with the Emotional Distress Scale ($p<0.05$). Improvement in global quality of life was greater for those patients treated with sertraline at week 26 than for those patients in the control group ($p<0.05$).
Choi-Kwon et al. 2006 **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	152 stroke patients with one of post stroke depression (average = 14 months post stroke), emotional incontinence or anger proneness. Individuals with SAH, severe communication problems, scored ≤23, or who had a history of depression prior to stroke	Participants enrolled in the study were randomly assigned to receive either treatment with fluoxetine 20 mg/day (n=76) or matching placebo (n=79) in a single morning dose. Treatment continued for a period of 3 months.	Primary outcomes were mean score on Beck Depression Inventory (BDI) for PSD, and percentage change in VAS score for emotional incontinence and anger proneness.	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		were not included.			condition. Treatment with fluoxetine was not associated with a significant improvement in depression when compared to the placebo condition at any of the follow-up evaluation points. Side effects: 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.
Sunami et al. 2012 **Non-randomised clinical trial**	N/A	19 inpatients with ischemic stroke with scores ≥40 on the Zung Self-rating Depression scale.	Patients were divided into two groups: 1) a treatment group which received fluvoxamine 25/mg p.o. o.d. on days 1 through 3, 50 mg on days 4 – 6 and 75 mg. from day 7 to the end of the trial period (n=9); 2) an untreated comparison group (n=10)	The ZSDS was administered at baseline and at 1,2 and 4 weeks.	At baseline, prior to treatment, the mean ZSDS score was 47.1±6.2. Over time, with treatment, mean scores were reduced. By week four, the mean score in the treatment group was 35.2±7.9 In the control group, symptoms of depression also appeared to improve over time. Mean SDS scores were 47.2±8.7 at baseline and 38.8 ±8.8 at 4 weeks. The authors do not provide the results of within group comparisons for baseline vs 4 weeks (rather, comparisons are reported incrementally within groups). In addition, between group comparisons are not reported.

**RCT included in the Cochrane systematic review and meta-analysis of pharmacotherapy.*

Heterocyclic Antidepressants

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lipsey et al. 1984* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	39 stroke patients assessed with mild depressive symptomatology at baseline. Initial assessment of depression was made via psychiatric interview and PSE	In a single daily dose (qhs), participants allocated to the treatment condition (n=17) were given 20 mg nortriptyline during the 1st week of treatment and 50 mg/qhs during week 2. Late-starters received 70 mg. during	Change in scores from baseline to end of treatment on HRSD and ZSDS; proportion of participants no longer meeting entry criteria for depression (DSM-III)	Patients who were treated with nortriptyline showed significantly greater improvement on the Hamilton Depression Scale, Zung Self-Rating Depression Scale; the Present State Examination and on the Overall Depression Scores than those who received the placebo treatment.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			week 1 and 100 mg, week 2. Overall doses started at 20 mg and was titrated up to 100 mg/qhs. Treatment lasted for a six week period. 22 patient were also allocated to a control condition and were provided with a matching placebo		
Robinson et al. 2000* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☑	104 adult individuals with previous stroke (within 6 months of study baseline). 48 individuals with no diagnosis of depression were enrolled in the study in order to assess effects of antidepressant use on recovery.	This study was originally designed as a randomized crossover trial. Patients were randomly assigned to either **fluoxetine** (10mg/d gradually increased to 40 mg/day) or **nortriptyline** (dose of 25 mg/day gradually increased to 100 mg/day) or identical **placebo** given over 12 weeks. Patients received 12 weeks of active treatments and crossed-over to 12 weeks of placebo treatment. However, as data from a significant number of participants assigned to the placebo condition "became ineligible for analysis" (31% response rate), an independent groups design was applied to the analysis	The Hamilton Rating Scale for Depression (HRSD-28) was used to assess depression at baseline and at each 3-week evaluation point. Successful response to treatment was defined as a >50% reduction in the HRSD scale score + failure to fulfill the criteria for major or minor depression.	**ITT analysis**: Overall, there was a significant time X treatment interaction identified ($F=3.45$, $df=8$, $p=0.004$). Post hoc analysis of this interaction demonstrated no significant difference between the nortriptyline and fluoxetine treatment groups at baseline; however, the placebo group appeared to have lower HRSD scores than the group assigned to treatment with nortriptyline ($p<0.05$). When the analysis was corrected for this difference, post hoc analysis demonstrated that individuals treated with nortriptyline had greater declines in HRSD scores than individuals treated with either fluoxetine or with placebo at 12 weeks follow-up. **Efficacy analysis**: Overall, at 12 weeks, there was a significant time X treatment interaction identified ($F=3.65$, $df=8$, $p=0.001$). Post hoc analysis demonstrated no between group differences on the initial evaluation; however, at 12 weeks, the nortriptyline group demonstrated lower HRSD scores than the fluoxetine group ($p<0.05$) as did the placebo group ($p<0.05$). The rate of successful treatment was 77% in the nortriptyline group, 14% in the fluoxetine group and 31% in the placebo condition. Neither depressed or non-depressed patients in either active treatment condition demonstrated significant greater improvement in functional recover than those assigned to placebo.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Adverse events: sedation, rash

**RCT included in the Cochrane systematic review and meta-analysis of pharmacotherapy.*

Selective Noradrenaline Reuptake Inhibitors (NARI)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Rampello et al. 2005 ***R*CT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT:☑	31 outpatients 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 (characterized by lethargy, slowness to initiate action and displaying anergia, hypokinesis and hypomimia). Mean age = 77.5± 4 years in the intervention group and 77.26 ±3.6 in the placebo group. Mean time since stroke was approximately 12 weeks.	Patients were randomly assigned to receive either treatment with the NARI, reboxetine (n=16) or a matching placebo (n=15). Individuals in the treatment condition received reboxetine 4 mg twice daily, once in the morning and once in the evening over a period of 16 weeks. Side effects reported by patients were recorded at each visit and patients were asked whether they remembered to take their medication regularly. Study Period = 16 weeks	Authors considered the following "parameters of efficacy": 1) variations in HRSD and BDI (Beck Depression Inventory) scores and 2) variations in the Synoptic Table Scores (where this was used to distinguish retarded from anxious depression). **Time points for assessment*: baseline, 4, 8 and 16 weeks.***	Patients in the treatment condition experienced significant improvement from baseline to 4, 8 & 16 weeks on both the Hamilton Rating Scale for Depression and the Beck Depression Inventory (test statistics not reported; p<0.01 for all comparisons). 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 (test statistics not reported; p<0.01 at 4, 8 and 16 weeks). **Patient reported side effects**: The most commonly reported side effects were dryness of faeces, constipation, hyperperspiration, hypotension and sinusal tachycardia. However, dryness of faeces, constipation, and hyperperspiration were all reported by similar numbers of individuals in the placebo condition. No patients dropped out of the study.

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Kucukalic et al. 2007	N/A	30 patients who developed symptoms of depressive disorder within 3 months of	All participants were treated with venlafaxine. 80% of subjects received	Primary study outcome was reduction of symptoms of depression as assessed by	There were significant reductions in depressive symptomatology at 1 and 3 months (p<0.001). At 1 month, there was notable improvement in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Single group intervention study		stroke. 20 patients were male. Mean age was 70.23 (SD=7.25). Most patients were assessed as experiencing moderate (36.7%) to significant (53.3%) depression using the clinical global impression scale (CGI) at baseline. HRSD at baseline = 25.2 (SD=5.48).	a daily dose of 75mg, the remainder were treated with a daily dose of 112.5 mg. Assessments included the 21-item Hamilton Rating Scale for Depression (HRSD), and the Clinical Global Impressions Scale (CGI). Length of treatment:3 months	the HRSD. Remission of depression was defined as a reduction in HRSD to a score less than 8. Clinical response was defined as a reduction of in HRSD score of ≥50% when compared to baseline. **Assessment points**: Baseline, one month and three months.	80% of patients and after 3 months of treatment, there was a clinical response (reduction of ≥ 50%) in 53.3% of patients and remission of depression in 26.6%. There was no comparison reported in terms of dosage received. CGI ratings for therapeutic effectiveness were 4.1 (SD=0.71) at 1 month and 4.73 (SD=0.58) at 3 months which ranges from moderately favourable to significantly favourable in interpretation. **Adverse events**: Mean (SD) ratings for unwanted effects on the CGI were 1.06 (SD=0.25) at 1 and 3 months. Two patients reported side effects (increase in blood pressure), but these were mild and transient.
Yamakawa et al. 2005 **Open label, case control study with an historical control group)**	N/A	11 stroke inpatients (from a group of 17) diagnosed with post-stroke depression agreed to be treated with milnacipran as part of the study.	11 patients were treated with milnacipran 30 mg/day X 1 week and then 60 mg/day for 1 week. Treatment continued until hospital discharge. Historical data from age-, sex- and severity of depression-matched patients hospitalized in 2001, and who were not treated with antidepressants, were used as a historical control group (n=11).	Zung self-rating depression scale (ZSDS) was used to assess severity of depression. In additional, patients completed the QUIK (a health-related QOL questionnaire).	Mean ZSDS scores were 52±7.8 for the treatment group and 52.9±4.6 in the historical control group. At discharge, mean ZSDS scores had decreased in the treatment group (44.7±11.1), but increased slightly in the control group (57.3±7.2). A two-way ANOVA demonstrated a significant group X time interaction, suggesting that treatment with milnacipran may be effective when compared to an untreated, historical control group. Side effects: None were reported.
Dahmen et al. 1999 **Single group intervention study**	N/A	12 patients who had experienced ischemic stroke within 2 weeks of study entry. All patients had been diagnosed with major depressive disorder according to the DSM-IV criteria (with the exception of the time criterion). 50% of patients were female.	All patients were treated with 75 mg venlafaxine per day for the first 2 days of treatment and 150 mg per day for the remainder of the study period. Assessments included the HRSD, MADRS, European Stroke Scale, Rankin	**Primary study outcome** was reduction in depressive symptomatology. This was assessed using the Hamilton Rating Scale for Depression (HRSD) and the Montgomery Asberg Depression Rating Scale (MADRS). Positive treatment response was	At 2 weeks, there was a positive treatment response recorded in 10/12 patients (reduction of ≥ 50% on HRDS). Scores on the MADRS showed a similar response. Mean HRSD scores were 24.3±3.2 at baseline and 7.25±2.2 after 5 weeks of treatment. Similar improvements were demonstrated using the MADRS scale for assessment. **Adverse events**: Treatment was well tolerated

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		Mean age was 66 ±12 years.	Scale, and Modified Barthel Index. Length of treatment: 5 weeks.	defined as a reduction in HRSD scores of >50%. **Assessment points**: Baseline, 2 weeks and 5 weeks.	and treatment was not discontinued in any cases. There were no cardiovascular or hepatic disturbances recorded with the exception of one case of elevated liver enzymes in one patient with chronic hepatitis.

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) vs. Selective Serotonin Reuptake Inhibitors (SSRIs)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Karaiskos et al. 2012 **Greece** **RCT**	CA: ☒ Blinding patient: ☒ Therapist ☒ assessor: ☒ ITT: ☒	60 patients diagnosed with post-stroke depression following a first-ever stroke within 12-months of study recruitment. **Exclusion criteria**: history of a major psychiatric disorder, atherosclerotic disease or history of angioplasty/bypass surgery, another major medical illness, degenerative and progressive neurological disease, or severe cognitive impairment.	Participants were randomized to receive duloxetine (titrated from 30 to 60-120 mg/day; n=20), citalopram (20-40 mg/day; n=20), or sertraline (50-200 mg/day; n=20). **Treatment Duration:** 3 months.	Depression was assessed with the Hamilton Rating Scale for Depression and Anxiety (HRS). Additional measures included the Mini-Mental State Exam, the modified Rankin Scale, and the Fatigue Severity Scale. **Timing of assessment:** Baseline, and at 1, 2, and 3 months following treatment initiation.	Participants in all three treatment conditions experienced significant reductions in depression ($p<0.01$) and anxiety ($p<0.01$) symptoms during the study period. Participants who received duloxetine experienced a significantly greater reduction in anxiety symptoms than did those who received citalopram ($p<0.01$) or sertraline ($p<0.01$). Mean HRS depression scores from baseline to study end: Duloxetine: 24.5 (7.5) to 3.4 (1.5) Citalopram: 23.7 (6.7) to 3.9 (2.0) Sertraline: 23.8 (7.3) to 4.2 (1.7) Mean HRS anxiety scores from baseline to study end: Duloxetine: 11.9 (2.1) to 4.3 (1.7) Citalopram: 11.6 (2.5) to 8.4 (0.6) Sertraline: 12.1 (2.9) to 8.7 (1.5) The rate of adverse events, including nausea, somnolence, dry mouth, and diarrhea, did not differ significantly between groups.
Cravello et al. 2009 **Open-label RCT**	CA: ☒ Blinding: Patient ☒	50 adults with a first-ever stroke within 12 months of study baseline and a diagnosis of a major depressive-like episode	Participants were randomly assigned to receive either 20 – 40 mg/day fluoxetine (n=25) or 75-150 mg/day	HRSD scores were obtained at baseline and after 1, 2, 4, 6 and 8 weeks of treatment. As this was a study of alexithymia, the	Overall, HRSD scores changed significantly over time ($F=39.5$, $df=5$, $p<0.001$); however, there was no significant timeXtreatment interaction reported. However, the use of venlafaxine appeared to have a significantly greater effect in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	Therapist ☒ Assessor ☑ ITT:☑	following the stroke. Individuals with severe cognitive impairment (assessed on the MMSE) were not included in the study.	venlafaxine SR. Therapy started and the lowest dose and was titrated upward as required. The dose could be doubled at the end of 4 weeks on the basis of non-response (assessed via CGI).	TAS-20 was also administered.	terms of reduction in the severity of the symptoms of alexithymia than did treatment with fluoxetine. Side effects associated with fluoxetine: insomnia, nausea, fatigability, cephalalgia and dizziness (all mild). Side effects associated with venlafaxine: headache, insomnia, dry mouth, agitation, sweating and urinary retention (all mild).

Gamma Aminobutyric Acid Compounds (GABA)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Robinson et al. 2008 **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 age was 66.8 (±13), 64.7 (±11.9) and 68.1 (±11.9) 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: i) 600 mg nefiracetam (n=55), ii) 900 mg nefiracetam (n=48) or iii) matching placebo. Capsules (both drug and placebo) were administered as 150mg doses twice per day to accommodate the 6-hour half-life of nefiracetam. Assessments included the HRSD, the Beck Depression Inventory (BDI), the Modified Mini Mental State examination, the Functional Independence Measure (FIM) and the NIH Stroke Scale (NIHSS). ITT analyses were completed in all patients. Per protocol analyses	Primary outcome was the change in depression severity as assessed on the Hamilton Rating Scale for Depression (HRSD). **Assessment points**: Baseline, 4 weeks, 9 weeks and 12 weeks.	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. Remission rates (HRSD scores of 8 or less at the end of treatment) were 41.2%, 43.6% and 40.5% for the 900, 600 mg and placebo groups, respectively. **Adverse Events**: No assessment of adverse events was reported.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			were also undertaken for all participants who completed at least 4 weeks of treatment. Length of treatment: 12 weeks		

Serotonin Agonist and Reuptake Inhibitors (SARI)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Reding et al. 1986* **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☒ ITT: ☒	27 patients with or without depression and enrolled in an inpatient stroke rehabilitation program. Patients with a history of recent MI or currently prescribed an antiarrhythmic medication were excluded from participation. Diagnosis of depression was based on DSM-III criteria for major depression or dysthymic disorder.	Participants were randomly assigned to receive either trazodone Hcl or placebo. Treatment with trazodone began at a dose of 50 mg po qhs and was increased by one capsule every 3 days until a dose of 200 mg was reached. This dosage was maintained for the remainder of the inpatient rehabilitation stay.	Primary study outcome was function assessed using the Barthel Index (every 2 weeks throughout the patient's rehabilitation stay).	For patients with a clinical diagnosis of depression at baseline, there was a greater improvement in Barthel Index scores over time among individuals assigned to treatment vs. those assigned to placebo (mean scores = 28±7 vs. 20±7). However, this difference did not reach statistical significance. Among individuals with an abnormal DST test at baseline, there was a statistically significant between group difference in mean improvement in BI scores over time, such that treatment with trazodone appeared to be associated with greater improvement among individuals with abnormal DST results. Side effects: The study was discontinued due to perceived side effects of 6 patients in the placebo group AND 6 patients in the trazodone group. In the trazodone group, these effects included sedation, and eye discomfort.
Raffaele et al. 1996	CA: ☒	22 patients enrolled in a stroke rehabilitation program	Individual participants were randomly assigned	Patients were assessed on the Barthel Index (the	Within groups analysis demonstrated a significant change over time on ZSDS scores in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	Blinding: Patient ☑ Therapist ☒ Assessor ☒ ITT: ☒	with or without a diagnosis of PSD. Individuals with aphasia were excluded from the study. Diagnosis of depression was made according to DSM-III criteria.	to receive either 300 mg/day of trazodone Hcl beginning approximately 30 days post-stroke for a period of 45 days or to a placebo condition. Individuals in the placebo group were observed for a total of 30 days.	primary interest was participation in the rehabilitation program), as well as on the Zung SDS. DST tests (a marker for depression) and cortisol serum tests were also administered.	individuals treated with trazodone (p=0.0004), but not in individuals assigned to the placebo condition. In addition, individuals treated with trazodone demonstrated significant improvement over time in functional ability assessed using the BI (p=0.0001), whereas individuals in the placebo condition did not. However, no direct. Between group comparisons were reported. Individuals with abnormal DST tests at baseline and who were treated with trazodone also demonstrated significant improvement in both symptoms of depression and functional outcome. Side effects: 7 patients in the placebo condition and 6 in the trazodone group reported GI side effects.

**RCT included in the Cochrane systematic review and meta-analysis of pharmacotherapy.*

Psychostimulants for Post-Stroke Depression

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Grade et al. 1998 **RCT**	CA: ☒ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	21 individuals with stroke who had been admitted to a community-based rehab unit. Patients with severe cognitive impairment (unable to understand or comply with instruction) were excluded from participation.	Patients were randomly assigned to treatment with either 5mg in the morning & 30mg before bedtime of methylphenidate (n=10) or a matching placebo (n=11). Treatment was continued for a period of 3 weeks.	Depression/symptoms of depression was assessed using the HRSD (25 item) and the Zung SDS. Cognitive status, motor function and ADLs were also evaluated. Side effects were assessed via checklist.	ANCOVA analysis of improvement over time demonstrated that patients receiving methylphenidate scored lower on HAM-D (p=0.028) and the Zung scale (p=0.055), as well as higher on the motor-FIM (p=0.032). While scores on the FMA were higher in the treatment group, they did not reach significance (p=0.075). This was accounted for, in part, by a ceiling effect demonstrated among individuals whose initial FMA scores were >80. There were no significant between group differences demonstrated on the MMSE (p=0.54) or in terms of number of side effects reported (p=0.94).

Risks and Possible Adverse Events Associated with Pharmacotherapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Loke et al. 2008 **Meta-Analysis**	N/A	4 studies (3 case-control and 1 cohort study) representing a total of 153 000 patients.	Included studies were controlled observational studies reporting the prevalence of upper gastrointestinal haemorrhage (UGIH) following treatment with SSRIs, NSAIDs, and their combined use.	Odds ratios and number needed to harm (NNT) were used to summarize the risk of UGIH associated with use of SSRIs, NSAIDs, and their combined use.	The odds ratio was 2.36 (95% CI:1.44-3.85; $p < 0.01$) and 3.16 (95% CI: 2.40 – 4.18) for risk of UGIH associated with use of SSRIs and NSAIDs, respectively. An additive interaction was observed for the combined use of SSRIs and NSAIDs, with an odds ratio of 6.33 (95% CI:3.40-11.8; $p < 0.01$) for risk of UGIH. For patients 50 years or older with no UGIH risk factors, the Number-Needed-to-Harm per year was 411 for SSRIs and 106 for the combined use of SSRIs and NSAIDs, although the NNH varies considerably with baseline risk.
Ried et al. 2011 US **Retrospective Cohort Study**	N/A	870 stroke patients, with and without a diagnosis of depression.	Medical records were reviewed for a cohort of patients diagnosed with stroke over a 1-year period. Data regarding comorbidities, depression diagnosis, and treatment were extracted for 6 months before and 1 year post stroke. Patients were followed for a total of 7-years.	Time from the stroke index date to mortality over the 7-year follow up period.	Depression diagnosis was associated with an increased risk of mortality (HR = 1.87: 95% CI 1.24-2.82). Patients were 3 times more likely to die if they had been treated for depression with SSRIs only before their stroke (HR = 3.12; 95% CI 1.60-6.09). SSRI treatment before and after resulted in a longer average survival rate compared with no SSRI treatment during the year following the stroke (HR = 0.31; 95% CI 0.11-0.86). However, the survival curves crossed over and SSRI treatment both pre and post stroke resulted in greater risk at the end of the 7 year follow up (HR = 1.36; 95% CI 1.0-1.87).
Coupland et al. 2011 **UK** **Population based cohort study**	N/A	60,746 primary care patients (ages 65 -100) with a new diagnosis of depression	570 general practices in the UK provided data regarding pharmacological treatment of depression and selected outcomes.	Hazard ratios associated with antidepressant use for: all-cause mortality, attempted suicide/self-harm, falls, MI, Stroke/TIA, fractures, Upper GI bleeds, seizures, road traffic accidents, adverse drug reactions, and hyponatraemia.	SSRIs were the most commonly prescribed drug class (54.7%) and were associated with the highest hazard rations for falls and hyponatraemia, as compared to patients who were not prescribed antidepressants. Use of antidepressants other than SSRIs and tricyclic antidepressants were associated with the highest risk for mortality, attempted suicide/self-harm, stroke/TIA, fractures, and seizures, as compared to those not prescribed antidepressants. Tricyclic antidepressants did not have the highest hazard ratio for any of the outcome measures. The absolute risk of all-cause mortality over 1 year was 7.04% for patients not taking any antidepressants, 8.12% for those on tricyclic antidepressants, 10.61% for

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					SSRIs, and 11.43% for other antidepressants. For individual drugs, trazodone, mirtazapine, and venlafaxine were associated with an increased risk for some outcomes.
Wu et al. 2011 **Taiwan** **Case Crossover study**	N/A	24,214 patients diagnosed with stroke enrolled in the national Health Insurance Research Database from 1998 to 2007	The rates of antidepressant use were compared during case and control time windows of 7, 14, and 28 days.	Odds ratio of stroke risk	The odds ratio of stroke risk with antidepressant use was 1.48 (95% CI =1.37-1.59). Stroke risk was negatively associated with the number of antidepressant prescriptions reported. SSRIs use was associated with a greater risk of stroke than the use of other antidepressants.

Adjunct Therapies

Light Therapy + Pharmacotherapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Tuunainen et al. 2009 **Meta-analysis (Cochrane review)**	N/A	20 studies (49 reports, total n=620) of RCTs examining the use of all forms of bright light therapy (timing, intensity, duration of exposure and type of device) either alone or in combination with drug therapy and compared to placebo/inactive treatment. Participants all had a diagnosis of non-seasonal depression – there were no restrictions on gender or	Data was extracted and quality assessment conducted by two reviewers. Authors were contacted for additional information when necessary. Publication bias was addressed using funnel plot analysis. Pooled analyses were conducted using Cochrane Review Manager software. Weighted Mean Difference (WMD) and	Principal outcomes of interest were identified as: level of depressive symptomatology, adverse effects associated with treatment, acceptability of treatment, deterioration of mental status or relapse during treatment, overall clinical improvement, quality of life, cost effectiveness and long-term follow-up.	18/20 studies took place in inpatient settings (hospital or long-term care facilities). Participants were more often female than male with a mean age of 50 years. The majority of participants were diagnosed with MDD. Treatment response (depressive symptoms) was based on 18 studies. Using the random effects model, bright light treatment was associated with a non-significant trend toward reduction in symptoms (SMD=-0.22, 95% CI -0.52, 0.09). However, when considering short term studies (less than 8 days) of high methodological quality only, response to bright light therapy was significantly greater than to placebo/inactive

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		age. Minor depression, bipolar depression and other depressive conditions were included in addition to major depressive disorder (MDD). *Did not include studies of individuals with post stroke depression.*	Standardized Mean Difference (SMD) estimates were calculated as appropriate for continuous outcomes. For dichotomous data, pooled relative risk ratios were calculated. Fixed effects models were used when significant heterogeneity ($p<0.05$) was identified in the analysis of both continuous and dichotomous data.		therapy (SMD = -0.90, 95% CI=-1.5, -0.31) and in those studies offering morning therapy (SMD=-0.38, 95% CI -0.62, -0.14). Evaluation of studies examining light therapy in combination with pharmacotherapy only (14 studies) revealed a significant effect in favour of bright light vs. control (SMD=-0.25, 95% CI -0.47 to -0.02). The authors conclude that bright light therapy, administered during the first week of treatment, offers promising antidepressant efficacy. **Adverse Events**: Reporting quality was judged to be poor overall; studies were short, underpowered and did not report outcomes with sufficient detail. Few studies provided a standardised assessment of adverse events. However, evaluation of hypomania was reported in a total of 7 studies. Bright light therapy was associated with increased risk (RR=4.91, 95% CI 1.66, 14.46; NNH = 8 95% CI 5,20). Headaches were also more common among participants receiving bright light therapy, but this was not statistically significant (RR=2.26, 95% CI 0.92, 5.59; 3 studies).
Sondergaard et al. 2006 **RCT**	CA: ☒ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☒	63 patients with *acute stroke* who were diagnosed with major depression based on an assessment by a psychiatrist in accordance with the DSM-IV.	All patients were given a fixed dose of citalopram (20 mg) per day for a period of 4 weeks. Patient participants were randomly assigned to receive either high or medium intensity light therapy. High intensity therapy was 10,000 lux daily at a distance of 30 cm while medium intensity treatment was defined as 4,000 lux daily at a distance of 60 cm. Light therapy was conducted every morning for 30 minutes over 14 days.	Primary study outcome was reduction of depression scores from baseline to week 4 on the Hamilton Rating Scale for Depression (both the 6 and 17 item versions of the HRSD were used). The Bech-Rafaelsen Melancholia Scale (MES) was also administered. ***Time points for assessment: Baseline, 2 and 4 weeks.***	All patients experienced similar reductions in reported symptoms of depression over the first 2 weeks of treatment, in both groups. At two weeks, there were no significant between group differences reported on any of the three outcome measures (HRSD-6, HRSD-17 or MES). At 4 weeks, however, there was a statistically significant reduction in depressive symptomatology on the HRSD-6 only in favour of the high intensity light treatment vs. moderate intensity (6.0 ± 3.0 vs. 4.4 ± 2.7, $p<0.05$). Although the differences did not reach statistical significance, bright light therapy was associated with greater reduction in depressive symptomatology on each of the other scales as well: 9.4±4.2 vs. 7.7±4.1 (HRSD-17) and 9.1±4.4 vs. 7.1±4.2 (MES). **Adverse Events**: The authors did not provide a standardized assessment of adverse events. There were no significant side effects reported and no patients left the study due to side effects.

Talk-based Psychotherapy + Pharmacotherapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mitchell et al. 2009 **RCT**	CA: ☒ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☑	101 patients *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 = 57 (range = 25-88 years). 59% of participants were male and had moderate ischemic stroke. Approximately 70% reported one episode of pre-stroke depression.	Patients were allocated to receive either a brief psychosocial, **problem-solving intervention** + possible antidepressant medication or usual care + possible antidepressant medication. 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. Family members and informal carers were encouraged to participate in these sessions. Patients allocated to usual care were treated by stroke care provider and participated in regularly scheduled follow-ups at 9 & 21 weeks post study entry and at 12 and 24 months post stroke. Patients in both groups could be prescribed antidepressant medication as deemed appropriate by their healthcare provider. Sertraline was the	Primary study outcome was reduction in the severity of symptoms of depression as assess using the Hamilton Rating Scale for Depression (HRSD) *at 12 months post stroke*. Additional assessments administered at 9 and 21 weeks post study entry and 12 and 24 months post stroke included the Stroke Impact Scale, the Geriatric Depression Scale and the Sense of Competence Scale (caregivers only). (Mitchell et al. 2008)	Immediately following the intervention (9 weeks), there was a significant difference, also in favour of treatment (-9.8±4.9 vs. -3.6±5.6, T=-5.78, p<0.001). At one year (the primary study outcome), the mean decrease in symptoms of depression assessed on the HRSD was significantly greater in the treatment group than in the control group (-9.2±5.7 vs. -6.2±6.4, T=-2.32, p=0.023). At 24 months, there was no longer a significant difference between groups. Using an HRSD≤9, as a cut-off for remission of depression, assignment to the treatment condition was associated with a significantly greater odds for remission immediately following treatment (OR=4.8, 95% CI 1.8, 12.9, p=0.001) and at 12 months (OR=2.7, 95% CI 1.1, 6.6, p=0.031). As for reduction in depressive symptomatology, however, this significant effect in favour of treatment was not reported at the 24-month assessment point. 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. Only 11% of prescriptions were tricyclic antidepressants, the most common of which was amitriptyline.

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			recommended first choice of possible medications. Medication use was tracked using a medication diary.		
Alexopoulos et al. 2012 **RCT**	CA:☒ Blinding: Patient ☒ Therapist ☒ Assessor ☒ ITT:☑	24 individuals diagnosed with post stroke depression (via SCI for DSM-IV-TR), MMSE ≥20. Individuals with mild to moderate aphasia could be included in the study. 58.3% of participants were male. Mean age = 70.9 ±8.5 years. Patients were recruited during inpatient rehabilitation following stroke	Participants were randomly assigned to receive either ecosystem focused therapy (EFT) or education on stroke and depression (ESD). EFT was provided in 12 weekly sessions of approximately 45 minutes in length. Inpatients had the first session prior to discharge; the remaining sessions were conducted in the participants' homes. EFT uses an integrated, educational, problem-solving approach to work through 5 therapy components – 1) provide an action-oriented perspective to recovery; 2) form a treatment "adherence enhancement structure" 3) provide a "problem solving structure" 4) help the family "re-engineer" to accommodate changed abilities and 5) coordinate with therapists and resources to develop a rehabilitation plan. Families and/or informal carers participated in	Primary study outcome was the reduction of depression and disability. Severity of depression was quantified using the HRSD. The WHODAS-II was also administered as an assessment of function. **Assessment Points**: Baseline, weekly during throughout the study.	Treatment X time analysis using a mixed effects linear model revealed an interaction suggesting that there was a trend toward greater decline in symptoms of depression associated with EFT vs. ESD or education (p=0.054). The mean HRSD score at 12 weeks was 8.2 (sd=6.63) for individuals in the intervention group and 13.2 (sd=5.37) for individuals assigned to the education control group. In addition, remission of depression was recorded for 8/12 participants receiving EFT (66.7%) vs. 2/12 (16/7%) participants in the education group (OR = 10, 95% CI 1.44, 69.26). The standardized between group effect size at the end of the intervention was 0.83 (95%CI =0.07, 1.72). In terms of disability, assignment to the EFT group was associated with greater gains in function over time (p=0.015). At 12 weeks, the standardized effect size between groups was 0.53 (95% CI -0.36, 1.43). It should be noted that 7/12 patients in the EFT condition and 5/12 patients in the ESD condition were treated with antidepressants at some point during the 12-week intervention period.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			sessions on an as-needed basis. Four therapists were trained in both EFT and ESD. All sessions were audiotaped. **Duration of Intervention**: 12 weeks		
Lincoln and Flannaghan 2003 **RCT**	CA: ☑ Blinding: Patient ☒ Therapist ☒ 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 –	Primary outcome measures were the BDI and the WDI. Secondary outcomes included the EADL scale, LHS and a rating of satisfaction of care. **Assessment Points**: 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). It should be noted that 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 ($\chi^2=0.2$, $p=0.9$).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			tailored to individual participants. **Duration of Intervention**: 3 months.		

Active Care Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Williams et al. 2007 **RCT**	CA: ☑ Blinding: Patient ☒ Therapist ☒ Assessor ☑ ITT:☑	188 patients *between 1-2 months* of an ischemic stroke event and who were verified as depressed (mild or major) following a diagnostic interview based on the DSM-IV criteria. Mean age = 60 (±13 in the intervention group and ±11 in the control group).	Patients were randomly allocated to receive either the Activate-Initiate-Monitor (AIM) intervention or control conditions. The AIM intervention consisted of 3 steps: 1) activate stroke survivors to understand and accept the diagnosis of depression and its treatment (20-minute psycho-educational session at baseline) 2) initiate antidepressant medication (recommendation of an antidepressant using a treatment algorithm) 3) monitor treatment effectiveness (including dose adjustment and medication change as necessary via scripted bi-monthly telephone calls). The control condition consisted of usual care plus an	Primary study outcome was proportion of responders to treatment at 12 weeks, where response was defined as HRSD score <8 or a 50% or more decrease in HRSD score. Secondary outcomes included reduction in severity as measured by mean change in HRSD or PHQ-9 scores between baseline and 12 weeks. Patients were assessed via face-to-face interviews at 6 and 12 weeks for depression. Adverse events were assessed using standardized questionnaire administered via telephone calls.	Compared to control participants, patients receiving the AIM intervention were more likely to demonstrate the defined response on the HRSD (51% vs 30%, p=0.005). This significant difference in favour of intervention was confirmed on multivariate regression, controlling for the influence of important covariates (age, race, sex, presence of caregiver) (p=0.037). Significant between group differences emerged at 6 weeks and were maintained at 12. In terms of depression severity, the difference in mean change (intervention vs. control groups) from baseline to 12 weeks was not significant when assessed on the HRSD (-7.3 ±7.2 vs. -5.3±8.0; p=0.07). **Adverse Events**: Serious events were reported in 17 participants, but event rates were not significantly different between groups. 56% of patients assigned to the control condition also took antidepressant medication at some point during the 12-week study period. 15 participants in the intervention group reported antidepressant-related side effects that prompted a medication change and 4 individuals reported more than one such change. Thirty-nine medication-related effects were reported by these 15 individuals, the most common of which were sedation, sexual, gastrointestinal and

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			identical number of baseline and telephone sessions as were received by the treatment condition in order to control for an attention effect.		anxiety-related effects.

Pharmacotherapy and Stroke Recovery

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Chollet et al. 2011 **FLAME** **France** **RCT**	CA: ☑ Blinding: Patient ☑ Therapist ☑ Assessor ☑ ITT: ☒	118 patients with acute ischemic stroke. Exclusion criteria: age <18 or >55, severe disability (NIHSS>20), premorbid or current deficits that could interfere with assessment, current diagnosis of depression, or use of antidepressants in the month prior to recruitment.	Participants were randomized 5-10 days post-stroke to receive fluoxetine (20 mg/day; n=59) or placebo (n=59) for 90 days. All participants received physiotherapy and standard inpatient stroke care during the study period.	Primary outcome: Fugl-Meyer Motor Scale (FMMS). Secondary outcomes: National Institutes of Health Stroke Scale, modified Rankin Scale, and the Montgomery Asberg Depression Ration Scale. **Timing of assessment**: baseline and at 30 and 90 days.	At the end of the 90-day treatment period, participants who received fluoxetine demonstrated significantly more improvement on the FMMS, as compared to those in the placebo group, controlling for centre, age, history of stroke, and baseline FMMS (adj. mean change=34.0 vs. 24.3, p=0.003). Between group comparisons of the upper limb and lower limb subscales of the FMM were both significant (p=0.002 and p=0.01, respectively). 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%). **Lost to follow-up**: 3.4% in the fluoxetine group and 5.1% in the placebo group.
Mead et al. 2012 **Cochrane Systematic Review and Meta-analysis**	N/A	56 RCTs (n=4060) comparing SSRIs to usual care or placebo in patients with stroke. Trials using a cross-over design, that compared	RCTs were identified through electronic and manual searching techniques and assessed for bias using the Cochrane Collaboration's risk of	**Primary outcome**: Disability and dependence at the end of treatment. **Secondary outcomes**: Impairment, depression, anxiety, quality of life, and	Dependency: On the basis of a single trial (FLAME), SSRIs were found to be significantly associated with reduced dependency (RR=0.81, 95% CI 0.68 to 0.97). Disability: On the basis of 22 trials (n=1310), a non-significant trend in favor of SSRIs was

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		different active treatments, or recruited participants with a mean time since stroke >12 months were excluded.	bias tool. Pooled analyses were conducted using random-effects models and summarized as risk ratios (RR) or standardized mean differences (SMD), as appropriate. Heterogeneity was assessed using the I2 statistic.	fatigue.	reported (SMD=0.92, 95% CI 0.62 to 1.23; I^2=85%). Neurological deficit: on the basis of 29 trials (n=2011), results significantly favoured SSRIs (SMD=-1.0, 95% CI -126 to -0.75; I^2=86%). Depression: Results favoured SSRIs whether based on continuous measures of depression (SMD=-1.91, 95% CI -2.34 to -1.48; I^2=95%) or dichotomous measures of depression (R=0.43, 95% CI 0.24 to 0.77 I^2=77%). Results were based on 39 (n=2728) and 8 trials (n=771), respectively.

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